HOUSE OF LORDS SESSION 2001–02

STEM CELL RESEARCH

REPORT FROM THE SELECT COMMITTEE

Ordered to be printed 13 February 2002

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(Q) refers to a question in oral evidence.
(p) refers to a page of written evidence.
The oral evidence supporting the Report is printed in a second volume, HL Paper 83(ii).

STEM CELL RESEARCH

13 FEBRUARY 2002

By the Select Committee appointed to consider and report on the issues connected with human cloning and stem cell research arising from the Human Fertilisation (Research Purposes) Regulations 2001

ORDERED TO REPORT

CHAPTER 1: INTRODUCTION

Background

1.1 The regulation of research on human embryos is governed by the Human Fertilisation and Embryology Act 1990. This legislation was enacted primarily to regulate the practice of *in vitro* fertilisation (IVF)[1] and the creation, use, storage and disposal of embryos formed by this means.

1.2 The regulatory authority established by the Act is the Human Fertilisation and Embryology Authority (HFEA), which is also empowered to issue licences, under strict conditions, for research on human embryos. The Act followed widespread discussion, both inside and outside Parliament, stimulated by the report of the Committee of Inquiry into Human Fertilisation and Embryology chaired by Baroness Warnock, which was set up in 1982 and reported in 1984.[2] The Act largely implemented the recommendations of the Warnock Committee.

1.3 Under the Act research on embryos older than fourteen days (or when the "primitive streak"[3] has appeared, if earlier) is prohibited. Research may not be undertaken except under a licence issued by the HFEA. Under Schedule 2 to the Act such a licence may not be granted "unless the Authority is satisfied that any proposed use of embryos is necessary for the purposes of the research;"[4] and "cannot authorise any activity unless it appears to the Authority to be necessary or desirable for the purposes of:

(a) promoting advances in the treatment of infertility,

(b) increasing knowledge about the causes of congenital disease,

(c) increasing knowledge about the causes of miscarriages,

(d) developing more effective techniques for contraception,

(e) developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation,

or for such other purposes as may be specified in regulations".[5]

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1 The fertilisation of a human egg by a human sperm outside the body.

2 Cmnd 9314.

3 A collection of cells from which the central nervous system eventually develops.

4 Paragraph 3(6).

5 Paragraph 3(2).

1.4 The Act limits these "other purposes" to projects of research "which increase knowledge about the creation and development of embryos, or about disease, or enable such knowledge to be applied".[6]

1.5 Licence applications therefore have to meet two tests: first that the use of embryos is necessary for the purposes of the research and they cannot be achieved by other means, such as work on animals; and, secondly—and only if the first test is satisfied—that the research is necessary or desirable for one of the specified purposes.

1.6 Since the Act was passed there have been a number of important developments—this is a very fast-moving area of science—which were not and could not have been foreseen at the time. The most significant was the cloning[7] in 1996 (by cell nuclear replacement—CNR[8]) of Dolly the sheep, which led to widespread concern that the same technique might be used to produce a baby. At the same time the cloning of Dolly enhanced interest in the feasibility of using CNR to develop treatment therapies.

1.7 The issues arising from these developments were looked at in 1998 jointly by the HFEA and the Human Genetics Advisory Commission (HGAC), which undertook a public consultation on human cloning. Their report recommended, among other things, that the Secretary of State for Health should consider specifying in regulations two further purposes for which the HFEA might issue licences for research: the development of methods of therapy for mitochondrial disease;[9] and the development of therapeutic treatments for diseased or damaged tissues or organs.[10]

1.8 In September 1999, following this report, the Government set up an expert group under the chairmanship of the Chief Medical Officer, Professor Sir Liam Donaldson, to undertake an assessment of the anticipated benefits of new areas of research using human embryos, the risks, and the alternatives; and to advise whether these new areas of research should be permitted and whether regulations needed to be made under the 1990 Act to extend the purposes for which the HFEA might issue licences for research involving human embryos.

1.9 In its report the expert group reviewed the scientific evidence. Its principal recommendation was that research using embryos (whether created by IVF or CNR) to increase understanding about human disease and disorders and their cell-based treatments should be permitted, subject to the controls in the 1990 Act.[11]

The Regulations

1.10 In the light of the expert group's report, the Government brought forward draft regulations extending the purposes for which research on human embryos could be lawfully undertaken (subject to licensing by the HFEA). What became the Human Fertilisation and Embryology (Research Purposes) Regulations 2001[12] were debated and passed by the House of Commons on 19 December 2000 and by the House of Lords on 22 January 2001. The Regulations added three new purposes to the five in the Act:

(a) increasing knowledge about the development of embryos,

(b) increasing knowledge about serious disease, or

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6 Schedule 2, paragraph 3(3).

7 The derivation from a cell or organism of another cell or organism genetically identical to it.

8 The procedure of replacing the cell nucleus of an egg with the nucleus from another cell.

9 The mitochondria are energy-producing structures in the cytoplasm (the jelly-like substance, which together with the nucleus it surrounds, forms the cell.

10 *Cloning Issues in Reproduction, Science and Medicine*, December 1998.

11 *Stem Cell Research: Medical Progress with Responsibility,* Department of Health, June 2000.

12 S1 2001 No. 188.

(c) enabling any such knowledge to be applied in developing treatments for serious disease.

1.11 Two points about the wording of the Regulations are worth noting. First, they refer to "serious" disease, whereas the Act itself refers simply to disease, and there is no definition of what constitutes serious disease. Secondly, they do not include among the purposes increasing knowledge about the creation of embryos, even though the Act invites an extension of the purposes in these terms. We comment on the drafting of the Regulations in Chapter 8.

1.12 In the debates on the Regulations particular concern was expressed about the prospect of the use of the CNR procedure to produce cloned human embryos, albeit for research rather than reproductive purposes. In the Lords an amendment was tabled by Lord Alton of Liverpool inviting the House to decline to approve the draft regulations until a Select Committee had reported on the issues connected with human cloning and stem cell research. This amendment was rejected (by 212 votes to 92). An alternative amendment was then proposed by Lord Walton of Detchant calling on the Government to support the appointment of a Select Committee to report on the issues connected with human cloning and stem cell research, and to undertake to review the Regulations following the report of that Committee. This amendment was passed without a division, and the Regulations duly came into effect on 31 January 2001.

1.13 Before the Regulations were made the Pro-Life Alliance applied for judicial review of them on two grounds. It submitted that they were *ultra vires* the 1990 Act (this claim was not pursued) and sought a declaration that an embryo created by CNR does not fall within the definition of embryo in the Act. The case was heard on 31 October and 1 November 2001. [13] Judgment was given in the High Court on 15 November 2001 granting a declaration in the terms sought.

1.14 The effect of the judgment was to remove embryos created by CNR from the controls imposed by the 1990 Act and regulation by the HFEA. The Government immediately announced that it would introduce legislation to prohibit reproductive cloning.[14] The Human Reproductive Cloning Bill was introduced on 21 November and became law on 4 December 2001. At the same time the Government appealed against the judgment to try to bring the use of CNR for research back within the scope of the Act. The appeal was heard on 16 January 2002 and judgment was given on 18 January: the Court of Appeal allowed the appeal and refused leave to petition the House of Lords. [15] The Pro-Life Alliance indicated that it would apply directly to the House of Lords for leave.

The establishment of the Committee and the scope of its remit

1.15 On 7 March 2001 the House of Lords agreed a motion appointing the Committee "to consider and report on the issues connected with human cloning and stem cell research arising from the Human Fertilisation and Embryology (Research Purposes) Regulations". The membership of the Committee is at Appendix 1, together with a list of the interests that the Members declared.

1.16 Sadly one member of the Committee, the Earl of Carnarvon, died during our inquiry, on 11 September 2001. He made a distinguished contribution in the many areas of public life in which he participated, and his work on the Committee was no exception: we have missed his sense of humour, his robust common-sense, and his unerring ability to get to the heart of the matter.

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[13] *R v. Secretary of State for Health*, ex parte *Bruno Quintavalle (on behalf of Pro-Life Alliance)* [2001], 15 November 2001.

[14] The implantation in a woman of an embryo created by CNR.

[15] *R (Quintavalle) v Secretary of State for Health [2002] EWCA, 18 January 2002.*

1.17 Our terms of reference focus on issues connected with the Regulations. We were clear from the outset that it was not our task to review the whole range of issues studied by the Warnock Committee. At the same time it is 17 years since the Committee reported, and we did not think that it would have been satisfactory simply to take that Committee's recommendations as given. We have therefore taken a fresh look at those aspects of its report relevant to our remit: in particular the fundamental question of the status of the embryo, which is central to the issues of stem cell research and cloning; and the creation of embryos for research, an issue on which the Warnock Committee was divided.

1.18 In reviewing the Regulations we have sought to take account of relevant developments in the field of reproductive technology and to assess whether the 1990 Act and the Regulations are still apt to cover them. We have looked very closely at the scientific issues—and have had the benefit of scientific advice—but we are not a scientific committee and we have seen our role as being to conduct a broadly-based examination of the ethical, legal and commercial as well as the scientific aspects of stem cell research.

1.19 The central question underlying the appointment of the Committee is whether the extension of the purposes in the 2001 Regulations is justified. In addressing this question the main issues we have considered are:

(a) the potential benefits of stem cell research;

(b) whether, in the current state of scientific knowledge, there are satisfactory alternatives to research on human embryos;

(c) the status of the early embryo;[16]

(d) the distinctions to be drawn, if any, between the use for research of "surplus" embryos (i.e. embryos left over from IVF treatment), of embryos created by IVF, and of embryos created by CNR;

(e) the commercial interests involved;

(f) the international context to the debate;

(g) the possible need for further legislation; and

(h) the possible need for further provision for the custody and regulation of stem cell "lines" derived from early embryos.[17]

Evidence

1.20 We issued a call for evidence on 5 April 2001 (reproduced at Appendix 2). We distributed it widely—not only to scientific and research organisations, the churches, medical charities, patients' support groups, pro-life groups and others with a close interest in the issues—but also to organisations representing sections of the general public, such as the National Association of Citizens Advice Bureaux, the Townswomen's Guild, the Trades Union Congress and the National Federation of Women's Institutes. These are profound issues which touch many people very deeply and we wanted to hear from as broad a cross section of society as possible.

1.21 We were also concerned to get as broad a view of the scientific issues as possible. We invited the major scientific and medical research organisations to give evidence, and their representatives included people working on both "adult" stem cells[18] and embryonic stem (ES) cells derived from animals; we wrote to scientists and medical practitioners cited as

[16] We use the term "early embryo" to describe the stage of embryonic development up to the appearance of the primitive streak—see paragraph 4.2(c).

[17] Stem cells cultured in the laboratory, which are able to reproduce themselves, in principle indefinitely.

[18] Stem cells obtained from the human body, rather than from an early embryo—see Chapters 2 and 3.

supporting the view that advances in work on adult stem cells made research on ES cells unnecessary and invited them to give evidence; and we made a special effort to obtain the views of some of the leading adult stem cell researchers around the world on the relative merits of adult and ES cells.

1.22 We received 52 submissions from representative organisations and 57 from individuals (listed in Appendix 3). We held 12 sessions of oral evidence at which 42 people representing 17 organisations (or in some cases giving evidence on their own account) appeared before us. In order to reach a broader range of opinion we also commissioned the Hansard Society to conduct on our behalf an internet debate over a period of four weeks in September and October 2001. One hundred and ninety six people registered to take part in the debate, 110 users logged on to the site and 330 messages were posted. A summary of the debate is included in the volume of evidence (pp 450-469). The nature of the submissions we received varied considerably, consisting of both technical evidence about scientific developments and expressions of opinion and argument on the ethical aspects. We received much valuable material of both kinds and are very grateful to all those who helped us by contributing their views.

1.23 We undertook two visits, one to the Medical Research Council's Clinical Sciences Centre at Hammersmith to gain a better understanding of the science involved, and the other to Durham University for an informal discussion with members of the multidisciplinary Policy, Ethics and Life Sciences Institute of the Universities of Durham and Newcastle. We followed the debates in other countries, particularly in the rest of Europe and in the United States. Some of us met members of the German *Bundestag* Commission of Inquiry on Law and Ethics in Modern Medicine and the European Parliament's Temporary Committee on Human Genetics, which were examining related issues, in the course of visits that they were making to the United Kingdom. We also obtained information from embassies here and from our diplomatic posts abroad about the situation in other countries; and we had a useful briefing from a number of the scientific attachés at British posts abroad.

Specialist advisers

1.24 We appointed two specialist advisers, Professor Roger Brownsword, Professor of Law at Sheffield University, and Professor Christopher Higgins, Director of the Medical Research Council's Clinical Sciences Centre, Imperial College Faculty of Medicine.[19] We are greatly indebted to both for the careful and impartial way in which they elucidated the complex scientific and legal issues with which we are concerned. The Members of the Committee are, of course, solely responsible for the conclusions of this report.

[19] See Appendix 1 for further details.

CHAPTER 2: STEM CELLS

2.1 In this Chapter we seek to explain what stem cells are, and assess the potential of stem cell research to generate new therapies. We then examine in Chapter 3 the relative scientific advantages and disadvantages of research on ES and adult stem cells.

What are stem cells?

2.2 In the human body new cells are generated by cell division. Most specialised cells do not themselves divide but are replenished, often via intermediate less specialised cell types, from populations of stem cells. Stem cells have the capacity to undergo an asymmetric division such that one of the two "daughter" cells retains the properties of the stem cell while the other begins to "differentiate" into a more specialised cell type (see Box 1 below). Stem cells are thus central to normal human growth and development, and are also a potential source of new cells for the regeneration of diseased or damaged tissue. Stem cells are found in the early embryo, in the foetus, in the placenta and umbilical cord, and in many (possibly most) tissues of the body. As stem cells from different tissues have different physical properties, they are difficult to identify by their physical characteristics alone. Stem cells from different tissues, and from different stages of human development, vary in the number and types of cells to which they normally give rise.

Box 1

Differentiation

In the course of human development a single cell, the fertilised egg, ultimately gives rise to more than 200 cell types (blood cells, neural (brain) cells, liver cells etc) which make up the human body. This process, whereby less specialised cells turn into more specialised cell types, is called "differentiation". As all cells in the body have (with few exceptions) the same genes, differentiation occurs, in large part, by switching on ("expressing") or switching off ("repressing") different subsets of these genes. Thus, differentiated cell types express different subsets of genes. For example, red blood cells express the gene making haemoglobin (the protein which carries oxygen around the body) but neural cells do not. In general as cells become more specialised (differentiated) the subset of genes that they can express becomes more restricted.

2.3 We describe in Chapter 4 the process of human embryonic development. At the earliest stages after fertilisation (up to about the eight cell stage) all the cells are "totipotent" (i.e. they have the capacity to develop into every type of cell needed for full human development, including the extra-embryonic tissues such as the placenta and umbilical cord). After about five days the blastocyst stage is reached. Within this ball of 50 to 100 cells there is the inner cell mass comprising about a quarter of the cells, from which a unique class of stem cells, embryonic stem cells (ES cells), can be derived. Unlike any other type of stem cell yet identified, ES cells have the innate capacity ("potential") to differentiate into each of the 200 or so cell types which make up the human body, and are described as "pluripotent". The potential of different types of stem cells is described in more detail in Box 2.

2.4 As development proceeds beyond the blastocyst, stem cells comprise a progressively decreasing proportion of cells in the embryo, foetus and human body. However, many, if not most, tissues in the foetus and human body contain stem cells which, in their normal location, have the potential to differentiate into a limited number of specific cell types in order to regenerate the tissue in which they normally reside. These stem cells, described as "multipotent", have a more restricted potential than ES cells, in that they normally give rise to some but not all the cell types present in the human body. Extra-embryonic tissues such as the placenta and umbilical cord also contain multipotent stem cells with the same genetic makeup as the cells of the embryo.

Box 2

The potential of stem cells

Stem cells from different sources differ in their potential for differentiation, i.e. in the number of cell types to which they can normally give rise. Stem cells which can give rise to all the cells required for human development, including extra-embryonic tissues, are described as "totipotent". Stem cells which can give rise to multiple, but not all, cell types are generally referred to as "multipotent". For example, haematopoietic (blood) stem cells from the bone marrow are multipotent as they give rise to the several different cell types present in blood but do not normally develop into e.g. neural cells. Sometimes the term "pluripotent" is used interchangeably with "multipotent" and this can cause confusion. We use "pluripotent" to refer to a stem cell which can give rise to every cell type in the human body, in contrast to "multipotent", which refers to stem cells which give rise to many, but not all, cell types in the body. As pluripotent cells cannot give to the extra-embryonic tissues they are not totipotent.

2.5 ES cells are a very specific class of stem cell which can be derived from the blastocyst. Other stem cells from later in the development of the early embryo or foetus, sometimes also (confusingly) referred to as embryonic stem cells, are not known to be pluripotent. Indeed, other embryonic, foetal and extra-embryonic stem cells are more akin to adult stem cells than to ES cells. (It has been suggested that it is more appropriate to refer to all stem cells in the body, whether embryonic, foetal or adult as "somatic" to distinguish them from ES cells.[20]) The use of different definitions, both in the scientific literature and in the evidence we received, can be confusing but is perhaps inevitable in a rapidly moving scientific field where hard and fast boundaries cannot always be drawn.[21]

The potential of stem cells for developing new therapies

2.6 Because of their ability to reproduce themselves, and to differentiate into other cell types, stem cells offer the prospect of developing cell-based treatments, both to repair or replace tissues damaged by fractures, burns and other injuries and to treat a wide range of very common degenerative diseases, such as Alzheimer's disease, cardiac failure, diabetes, and Parkinson's disease. These are some of the most common serious disorders, which affect millions of people in the United Kingdom alone, and for which there is at present no effective cure. Stem cell treatments, unlike most conventional drugs treatments, have the potential to become a life-long cure.

2.7 This potential has given stem cell research a high profile and is leading to significant interest and investment in academic, medical and commercial research throughout the world. The main funding bodies gave evidence on the level of their investment in stem cell research (much of it in work on animals):

(a) the Biotechnology and Biological Research Council has invested about £17 million in stem cell research over the last ten years (p 230);

(b) the Chief Executive of the Medical Research Council (MRC), Professor Sir George Radda, told us that the MRC gives stem cell research a very high strategic priority and supports it to the tune of about £4.5million a year (Q 128); and

(c) since 1995 the Wellcome Trust has awarded some 15 project and programme grants specifically for stem cell research, totalling about £4.5million. Although this is only

[20] See memorandum by Professor Angelo Vescovi (pp 473-475).

[21] This is exemplified in recent debate over the efficacy or otherwise of stem cell transplants for Parkinson's disease. A study in 2001 (reported in the *New England Journal of Medicine* (344:710-719)) suggesting that such a treatment had unwelcome side-effects has been cited by some as grounds for concern about the safety of embryonic stem cells. However, although these experiments were carried out with stem cells from an embryo, they were in fact from 7-8 week embryos and were therefore foetal and not ES cells.

just over half of one per cent of the total Trust spend, the Director of the Trust, Dr Mike Dexter, envisages many more applications in the future (Q 334).

Although the amounts so far invested are relatively modest, all the funding bodies saw this as a major growth area.

2.8 The simplest way of using stem cells for therapy is by implanting a tissue which contains appropriate stem cells into an individual in whom that tissue is diseased or damaged, so that the transplanted stem cells regenerate the various cell types of that tissue. This type of therapy is in routine clinical use for treating patients with leukaemia and other blood disorders by introducing haematopoietic stem cells, for example by bone marrow transplants. Despite the fact that such treatments have been successfully applied for about 20 years, few other examples of this type of approach have been developed. This is because the haematopoietic system is unusual in its accessibility and in the fact that it has evolved specifically to continuously replenish cells in the blood at high rates.

2.9 Recent scientific advances have opened up the possibility of treating a much wider range of disorders by isolating and growing stem cells in the laboratory. In some cases it may be possible to administer stem cells directly to an individual, in such a way that they would migrate to the correct site in the body and differentiate into the desired cell type in response to normal body signals. However, currently it seems more likely that stem cells will be grown and induced to differentiate into a defined cell type in the laboratory prior to implantation. In the longer term it may also be possible to induce stem cells to differentiate into several cell types, generating whole tissues, prior to implantation. For these approaches a much greater understanding of differentiation and developmental "signals" will be required.

2.10 None of our witnesses seriously questioned the therapeutic potential of stem cells for a wide range of disorders. There were differences of view as to when such therapies might be realised. Most witnesses believed that the introduction of effective stem-cell based therapies would be a gradual process over the next five to twenty years, requiring much basic and clinical research prior to clinical application. This is a normal time-span for the development of any new treatment. Even "conventional" drugs therapies take five to fifteen years and several hundred million pounds of investment to reach the patient.

The research path to therapeutic application

2.11 Any potential new treatment for disease requires a great deal of scientific and clinical research before it can be made available to patients. Three necessary steps can be distinguished. First, basic scientific research is required to establish what may or may not be possible, and to identify the best approaches to take and any pitfalls to be avoided. (The types of research questions which must be answered if stem cell therapies are to be developed effectively are set out in paragraph 2.13 below.) Secondly, pre-clinical studies in animals (normally mice) and small-scale clinical studies in human volunteers must be carried out to gain "proof of principle" for each new therapy and to ascertain whether it is safe and whether or not there may be significant side-effects. Thirdly, large-scale clinical trials are required to determine whether the therapy is of real clinical benefit and to further assess and assure safety. In the development of most therapies there is an iterative process between the first and second stages, during which blind alleys are eliminated and the best approaches refined. The great majority of potential stem cell-based therapies are still at the first stage of this process, basic scientific research.

2.12 Stem cell research is currently subject to very rapid change and our report can reflect only the current state of knowledge. From the evidence we have received we are clear that over the next few years most studies on stem cells, whether adult, foetal or embryonic in origin, will be basic research. This research will not in itself be therapeutic, but will be undertaken with the aim of gaining the understanding necessary if stem cells are to be used widely for therapeutic benefit. The potential for stem cell therapies to last the life of the individual patient makes it particularly important to ensure that any safety issues are identified and resolved satisfactorily. Only after considerable advances in understanding

processes such as the control of differentiation will it be possible fully and safely to exploit stem cells to treat or cure individuals.

2.13 There is unlikely to be a single approach to the use of stem cells in therapy: different disorders are likely to require different types of stem cell and different therapeutic approaches. For example, for some treatments it may be possible to transplant whole tissues without isolating stem cells (as with bone marrow transplants), whereas for others it may be more effective to purify and grow stem cells in the laboratory prior to differentiation and reimplantation. In order to exploit stem cells to the full it is likely to be necessary to:

(a) identify and characterise the specific stem cells to be used. Currently stem cells are primarily defined only by their biological function; if stem cells are to be isolated and purified for therapeutic purposes, scientists must be able to identify unique characteristics which will allow them to be isolated routinely, efficiently and reliably from amongst the millions of cells in a tissue;

(b) isolate and purify the required stem cells in sufficient numbers to be useful. Stem cells often form a very small proportion of cells in a tissue.

(c) grow stem cells in the laboratory under "clean" conditions so that they (or cells derived from them) can be transplanted back into patients; doctors must be certain that the properties of the cell have not changed in the laboratory, and that there are no contaminants that might cause harm if used to treat patients;

(d) show that stem cells, once isolated from their normal location and grown in the laboratory, do not undergo unwanted changes in their properties. For example, all stem cells have the potential to divide, and it is therefore important to ensure that any manipulation does not alter the control of this division process and create a risk of generating cancerous cells;

(e) "direct" stem cells to differentiate efficiently into specific cell type(s) required for therapeutic purposes, and ensure that this process does not give rise to any inappropriate cell type. Scientists still know little about the signals which direct differentiation;

(f) understand the differentiation process so that when a stem cell has been induced to differentiate into a specific cell type, scientists can be sure that that cell is indistinguishable from normal cells of the same type in the body and will integrate properly with them;

(g) understand the dedifferentiation process so that, if an adult stem cell is dedifferentiated to enhance its normal potential, scientists can be sure that this has been achieved accurately and that the signals it originally acquired during differentiation have been erased;

(h) understand how stem cells get to and remain in their proper location in the body, so that when they (or cells derived from them) are transplanted into the body they do not migrate to inappropriate locations;

(i) avoid immunological rejection of any implanted cells.

2.14 Until recently it has generally been considered that in mammalian cells the process of differentiation is irreversible. However, it has been demonstrated in animals that it is possible to reprogramme ("dedifferentiate") the genetic material of a differentiated adult cell by CNR (see Chapter 5). Following this seminal finding, many studies have also suggested that adult stem cells may have greater "plasticity"[22] than previously suspected: they may be reprogrammed to give rise to cell types to which they do not normally give rise in the body. The potential of specialised cells to differentiate into cell types other than those to which they normally give rise in the body is little short of a revolutionary concept in cell biology. It has significantly increased the possibilities for developing effective stem cell-based therapies.

[22] The capacity of a cell to develop into different cell types.

Box 3

Increased plasticity of adult stem cells

Recently it has been observed that some relatively specialised stem cells can be induced (at least under some conditions) to give rise to a wider range of cell types than had been expected. For example, it has been reported that stem cells from blood, which in the body normally give rise only to blood cells, can be induced to differentiate into neural cells. This process might occur in one of the following ways:

(a) the original stem cell might dedifferentiate to pluripotency and then be reprogrammed to generate the second cell type; or

(b) the original cell might change into the second cell type without going through a dedifferentiated intermediate stage, a process sometimes called "transdifferentiation".

Little is known about such increased "plasticity", which is based on observations from which plasticity is inferred rather than on an understanding of the processes involved.

Immunological rejection of stem cell-based therapies

2.15 Immunological rejection is a particularly important consideration for stem-cell based therapies. The human body possesses an immune system which recognises cells that are not its own and rejects them. The immune system has evolved primarily as a protection against micro-organisms that cause disease. However, the body also rejects human cells or tissues that do not belong to it. Immune rejection is one of the major causes of organ transplant failure and is one of the problems which will need to be overcome for any stem cell-based therapy to be effective. There are three main ways of avoiding or repressing immune rejection of transplanted cells or tissues:

(a) *The use of immuno-suppressant drugs*. These drugs have been refined over many years, as part of organ transplantation research. However, they are not always effective; they must normally be taken over the lifetime of the patient; and they leave the patient open to infection.

(b) *Using "matching" tissues*. Sometimes during transplantation it is possible to get a matched tissue type, usually from a near relative. This is often sought for bone marrow transplants. Finding a matching donor is unlikely to be a useful approach for most cell-based therapies. However, because stem cells can, in principle, be cultured indefinitely, it might be possible to establish stem cell banks of sufficient size to comprise stem cells with a reasonable (though never perfect) match to the majority of individuals in the population. If this proved possible, the appropriate matching stem cell from the bank could be selected and differentiated into the cell type required for therapy. Several thousand stem cell lines would be needed to obtain matches to the majority of the British population comparable with those achieved with matched bone marrow transplants.

(c) *Using the individual's own cells or tissues*. This would be the surest means of avoiding immune rejection. Adult stem cells isolated from an individual, and then used to treat him or her, offer one possible way of achieving this, although not in all circumstances. Alternatively CNR could be used to generate cells or tissues that match those of the patient, although it is generally thought that this approach is unlikely to provide the major therapeutic route (see Chapter 5).

CHAPTER 3: POTENTIAL ADVANTAGES AND LIMITATIONS OF ES CELLS AND ADULT STEM CELLS

3.1 We have received much evidence on the relative advantages and disadvantages of ES cells compared with adult stem cells for the development of stem cell-based therapies. The main scientific considerations are summarised in the following paragraphs.

ES cells

3.2 A great deal of research has been undertaken on ES cells from animals, particularly mice, over many years. In the last three or four years researchers around the world, including in Australia, India, Singapore, Sweden and the United States, have used similar methods to establish human ES cell lines from blastocysts. Three research licences have been granted by the HFEA (for purposes permitted by the 1990 Act) which could result in human ES cell lines being derived in the United Kingdom, but we were told that at the time of writing none had yet been derived.

Potential advantages

3.3 Research on mice has shown that it is possible to isolate pluripotent ES cells from the blastocyst, culture and multiply them in the laboratory, in principle indefinitely, and induce them to differentiate into a wide range of different cell types. Cultured ES cells from some mouse strains are routinely re-implanted into a blastocyst, and then into a mother, to give rise to normal offspring. This demonstrates that ES cells, at least those from mice, can be grown and manipulated safely in culture, and that they can generate all cell types in the body.

3.4 This research has shown that ES cells have significant potential for developing new therapies. First, they are at present the only stem cells that can be readily isolated and grown in culture in sufficient abundance to be useful. Secondly—at least for mice—they can be used to generate a normal animal, which indicates that they are unaltered and potentially safe for therapeutic use. Thirdly, ES cells have the potential to regenerate all normal cell types in the body—the only cell type currently known to have this potential (see paragraph 2.3). Finally, because ES cells are undifferentiated it is not necessary to dedifferentiate ES cells prior to differentiation into a new cell type.

Possible limitations

3.5 The most significant potential scientific limitation on the therapeutic use of ES cells is the problem of immune rejection. Because ES cells will not normally have been derived from the patient to be treated, they run the risk of rejection by the patient's immune system. Three main approaches to overcoming this problem were described in paragraph 2.15.

3.6 It has been argued that, because ES cells have the potential to differentiate into all cell types, it might be difficult to ensure that, when used therapeutically, they did not differentiate into unwanted cell types; or undergo chromosomal alterations which generated tumours. It is clearly essential to guard against these risks, but there is no reason to believe that this is a significantly greater risk for ES cells than for other stem cells.

3.7 Current methods for growing human ES cell lines in culture are adequate for research purposes, but the requirement for co-culture of human ES cells with animal materials necessary for growth and differentiation would preclude their use in therapy. This problem, which applies to all cells grown in culture, is unlikely to be insoluble.

Adult stem cells

3.8 The potential of adult stem cells for therapeutic application is illustrated by the use of haematopoietic stem cells to treat leukaemias and other blood disorders. As discussed in paragraph 2.8, this type of whole tissue transplant probably has limited general applicability. However, recent studies suggesting that various adult stem cells have much greater potential

for differentiation than previously suspected (see Box 3) have opened up the possibility that other routes to adult stem cell therapy might be available.

Potential advantages

3.9 The developments referred to above suggest that adult stem cells may have greater therapeutic potential than had previously been thought. Their most significant potential scientific advantage is that, at least for some disorders, they might be isolated from the individual to be treated and therefore avoid rejection by the immune system when transplanted back into that same individual for therapeutic purposes.

Possible limitations

3.10 Even if much of the potential of adult stem cells is realised, there are circumstances where they are unlikely to be useful. The isolation of some types of adult stem cells for therapy, for example the isolation of neural cells from a patient's brain, would be impractical. Similarly, where a person suffers from a genetic disorder or some types of cancers, adult stem cells isolated from that individual will retain the damaging genetic alterations underlying the disease and so be of little therapeutic value.

3.11 If adult stem cells are to be of general utility, it will be necessary to learn how to isolate them, grow them in culture and differentiate them into new cell types. The isolation and growth of adult stem cells have to date proved very difficult. Stem cells generally represent a very small proportion of cells in adult tissues. Unambiguous identification is difficult as their presence in a tissue or mixture of cells is generally inferred from a research observation rather than indicated by any specific biochemical marker which might aid their purification.[23] Although there are several reports of "enrichment"[24] of adult stem cells, there are few, if any, reports of adult stem cells being purified to homogeneity (i.e. where no other cell types are present). It has been suggested that some adult stem cells retain many of their characteristics only as a result of the presence of signals from other surrounding cells, and that maintenance in culture may therefore be difficult.

3.12 Current understanding of the potential of adult stem cells for redifferentiation is still very limited. Although many studies suggest that such processes occur, there is often a degree of ambiguity, for example whether or not the multiple new cell types arise directly from a single adult stem cell with increased potential for differentiation, or from several different stem cells each with a limited but different potential for differentiation. Moreover, it is not yet known whether adult stem cells give rise to cells of different tissue types by transdifferentiation, or by dedifferentiation to a pluripotent cell, which then differentiates into the new cell types (see Box 2).[25] The control and safety of dedifferentiation is a major challenge and one about which little is yet known (see paragraph 3.18).

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[23] For example, when an adult tissue is transplanted from one individual to another (normally carried out using mice), the transplanted tissue is observed to give rise to cells of a type not present in the original tissue. From this observation it is inferred that the transplanted tissue contains adult stem cells with the potential to differentiate into new cell types, but the stem cells themselves have not necessarily been identified or isolated.

[24] Increasing the proportion of stem cells in a sample by removing some of the non-stem cell material.

[25] Research by Dr I S Abuljadayel has been cited on several occasions, including in the Debate in the House of Lords on the Regulations (22 January 2001, Col 37) as supporting this proposition. As Dr Abuljadayel's work has not been published, we invited her to submit it to the Committee as evidence, which she kindly did (pp 296-306) along with other supporting material. Briefly Dr Abuljadayel claims that blood cells can be induced to dedifferentiate to a pluripotent stem cell (a process she calls "retrodifferentiation") which can then be directed to redifferentiate into different cell lineages. If this claim were borne out, it would be a major breakthrough. We have taken advice on Dr Abuljadayel's work and we are satisfied that it does not lead us to modify our conclusions. We note that her manuscript was submitted for publication to four of the leading scientific journals, but was not accepted for publication.

3.13 The efficiency of differentiation of transplanted adult stem cells is, to date, very poor. For example, although transplantation of bone marrow into mice suffering from muscular dystrophy can lead to new, repaired muscle fibres, the efficiency is several orders of magnitude below that which would be therapeutically useful. Much research is still required to determine whether the efficiency can be enhanced.

3.14 In their natural location in the body adult stem cells do not exhibit great potential for differentiation into new cell types but have evolved to give rise only to specific cell lineages. Indeed, if they exhibited increased potential or plasticity in their natural position in the body this would have disastrous consequences: the "wrong" cell types might develop into the "wrong" tissues. The feasibility of manipulating adult stem cells to undergo dedifferentiation and redifferentiation along pathways which they do not normally exhibit, and the consequences of doing so, are as yet uncertain.

Do developments on adult stem cells make research on ES cells unnecessary?

3.15 Research on adult stem cells is at a very early stage. Without a great deal of further research it will not be clear to what extent their therapeutic potential will be realised, or for what type and proportion of potential applications adult stem cells will be applicable. Although almost all the scientists who gave evidence to us were excited by recent studies on adult stem cells, most sounded a note of caution: many of the published studies are still open to multiple interpretations or require replication; and there are many crucial scientific issues to be resolved.

3.16 We received evidence from a number of individuals arguing that recent developments in research on adult stem cells demonstrated their therapeutic potential and made research on ES cells unnecessary.[26] However, the evidence from the great majority of scientific and medical research organisations, and the experts on adult stem cells whom we consulted, did not support that view. They did not see adult stem cells and ES cells as alternatives but as complementary pathways to therapy. They argued that relatively little is yet known, and that substantially more research on both adult and ES cells is needed before the best routes for therapies can be ascertained; that, despite increasing optimism, it is still not known to what extent it will be possible to exploit adult stem cells therapeutically and in the meantime other avenues should not be closed off; and that, even if much of the potential of adult stem cell-based therapies is realised, it is unlikely that adult stem cells will fulfil all therapeutic needs.

3.17 Although adult stem cells may ultimately fulfil many therapeutic needs, the strong weight of evidence is that the full potential of adult stem cell research and its therapeutic application is unlikely to be realised without research on ES cells. This is because, apart from CNR, ES cells provide the only realistic means at present of studying the mechanisms and control of the processes of differentiation and dedifferentiation. If stem cell therapies (whether using ES or adult stem cells) are to be of clinical benefit and of demonstrated safety, a much clearer understanding of these processes is required. The utility of ES cells for studying them is clearly demonstrated by advances made from animal studies. Most future studies probably can and will be undertaken using mouse (or other animal) ES cells rather than human ES cells. Nevertheless, if safe and reliable therapies are to be developed, a comparison with human ES cells must eventually be made.

3.18 ES are needed for this purpose, partly because of the relative ease with which they can be isolated, maintained in culture and differentiated into other cell types; and partly because they are the only fully undifferentiated pluripotent cell type available for study. If scientists are to dedifferentiate adult stem cells to pluripotency, prior to redifferentiation into a new cell type for therapeutic purposes, they must know whether they have done this correctly and whether the process is safe. Differentiation involves "marking" the genetic

[26] Notably from Dr Elizabeth Allan, who submitted a memorandum comprehensively documenting research studies involving adult stem cells (pp 306-359).

material in a number of ways. These "markings" (including chemical changes to the DNA and the interaction of specific proteins with it) are "remembered" during cell division. If an adult stem cell is to be dedifferentiated prior to redifferentiation for therapeutic purposes, these markings must be correctly erased. In fact it is not fully established that CNR produces complete differentiation and erasing of these markings, as recent discussion of Dolly the sheep illustrates.[27]

3.19 It may be that, in time, scientific understanding of the processes involved and developments in the manipulation of adult stem cells will make research on ES cells redundant. The Committee is not convinced that this point has yet been reached or will be reached in the near future. These issues were exhaustively considered in the United States last year by the National Institutes of Health. Its comprehensive report reviewed the state of the science as at 17 June 2001.[28] Emphasising that ES and adult stem cells are different, its concluding paragraph reads:

> Predicting the future of stem cell applications is impossible, particularly given the very early stage of the science of stem cell biology. To date, it is impossible to predict which stem cells—those derived from the embryo, the foetus, or the adult—or which methods for manipulating the cells, will best meet the needs of basic research and clinical applications. The answers clearly lie in conducting more research.

3.20 Because of the importance of this issue we also asked a number of internationally renowned adult stem cell experts for their views. We received replies from Professor Helen Blau, of the Stanford University School of Medicine, Dr Jonas Frisen, of the Karolinska Institute, Stockholm, Professor Nadia Rosenthal, of the European Molecular Biology Laboratory, Monterotondo-Scalo, and Professor Angelo Vescovi, Director of Research at the Stem Cell Research Institute, Milan. They are published in the volume of evidence (pp 472-478). They were unanimous that there was a need for research on both adult and ES cells. Dr Frisen expressed his view as follows:

> My opinion is that adult stem cells are clearly different from ES cells, and that there are no scientific data suggesting the opposite. Although I believe everyone would agree that it would be very good if adult stem cells had the same potential as embryonic, this is unfortunately today only wishful thinking. I find it very important today to work on both embryonic and adult stem cells. This will ensure that potential therapies are not delayed.

3.21 Of all the scientific issues relevant to our inquiry we have given more attention to recent developments in adult stem cell research than to any other. Scientific developments in this field are so rapid that it is difficult to make any firm predictions with confidence. This in itself suggests that avenues of research should not be closed off prematurely.

Conclusions

3.22 Based on the evidence we have heard our conclusions on the research and therapeutic potential of ES cells and adult stem cells are as follows:

(a) **stem cells appear to have great therapeutic potential for the treatment of many disorders that are both common and serious and for the repair of damaged tissue;**

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[27] Dolly was created by dedifferentiating an adult cell nucleus by inserting it into an egg from which the original nucleus had been removed. It is remarkable that this can be achieved at all, although it is still not known whether this dedifferentiation was "perfect". It has been suggested that some of the properties of the differentiated cell have not been fully erased and that the biological age of Dolly might therefore be greater than her birth age. The same caveats could be applied to dedifferentiation of adult stem cells.

[28] *Report on Stem Cell Research*, National Institutes of Health, 2001.

(b) **until recently most research on stem cells has focussed on ES cells from animals and the derivation of ES cell lines from them; cell lines from human ES cells have the potential to provide a basis for a wide range of therapies;**

(c) **recent research on adult stem cells, including stem cells from the placenta and umbilical cord, also holds promise of therapies; and research on them should be strongly encouraged by funding bodies and the Government;**

(d) **to ensure maximum medical benefit it is necessary to keep both routes to therapy open at present since neither alone is likely to meet all therapeutic needs;**

(e) **for the full therapeutic potential of stem cells, both adult and ES, to be realised, fundamental research on ES cells is necessary, particularly to understand the processes of cell differentiation and dedifferentiation;**

(f) **future developments might eventually make further research on ES cells unnecessary. This is unlikely in the foreseeable future; in the meantime there is a strong scientific and medical case for continued research on human ES cells.**

CHAPTER 4: THE STATUS OF THE EARLY EMBRYO

The development of the embryo

4.1 In such a sensitive area as research on human embryos, terminology is very important. Debate is often clouded by misconceptions of the stages of human development. The following paragraph outlines the various stages of embryonic development. A glossary of biological terms used in this report is at Appendix 5.

4.2 The development of the embryo is a continual process of change. For convenience it can be described in terms of the following seven stages:

(a) The female egg ("oocyte") is fertilised by the male sperm. The process of fertilisation consists of a number of steps which ultimately result in a single cell, the"zygote". The egg and sperm each carry half the genes of a normal cell. The zygote contains all the genes necessary for the development of an individual, half derived from the mother and half from the father. (As described in paragraph 5.15, a very small proportion of genes are contained in the mitochondria and are inherited exclusively from the mother.)

(b) The zygote undergoes a series of cell divisions starting some 36 hours after the beginning of fertilisation. Initially (up to the eight cell stage) all the cells are essentially identical and all have the potential, if placed in the right environment, to develop into an individual. Indeed, identical twins result from the splitting of the cells at this early stage: they are genetically identical as a result of developing from the same fertilised egg. One or more cells can be removed from the zygote at this stage without impairing development. This is illustrated in preimplantation diagnosis during IVF (which in the United Kingdom is permitted only to prevent serious genetic disease) in which a single cell is removed at the eight cell stage for genetic analysis. The remaining seven cell zygote can be implanted and develop normally.

(c) When the developing embryo reaches about 100 cells (still smaller than a pinhead) it is known as a blastocyst. The blastocyst is a small hollow ball of relatively undifferentiated cells. Many of the cells in the blastocyst go on to develop into non-embryonic tissues such as the placenta or umbilical cord. However, within the blastocyst is a population of cells, the inner cell mass, from which ES cells can be derived and from which the embryo itself develops. The properties of ES cells were described in Chapter 2. As the source of ES cells, the blastocyst is the primary focus of much of the debate on the use of embryos in stem cell research and therapy. It is sometimes referred to as the preimplantation embryo. In this report we use the term "early embryo" to cover stages of development up to the appearance of the primitive streak (see (e) below).

(d) About a week after fertilisation implantation of the blastocyst in the womb takes place. If implantation does not take place, the blastocyst does not develop further: it does not go through the stages of embryonic development, and cannot become a foetus; specific biochemical signals from the mother are required for further development. A substantial proportion of early embryos—many estimates put it as high as 75 per cent—are naturally lost before implantation. At this stage the cells are still relatively undifferentiated and there is no trace of human structure such as a nervous system, and hence there can be no sentience.

(e) At about 14 days after fertilisation, following implantation, the early embryo consists of about 2000 cells. It is only at this stage that the cells begin to become differentiated into more specialised cell types, and the "primitive streak", from which the central nervous system eventually develops, begins to appear.

(f) After about seven weeks' development, individual organs become recognisable and the embryo can properly be described as a foetus.

(g) At around nine months, given normal gestation, the baby is born.

The status of the early embryo

4.3 The starting point for consideration of the ethics of research on human embryos is the status of the early embryo. This was one of the most fundamental questions facing the Committee since it is intimately bound up with the questions of when human life begins and of the definition of a person.

The Warnock Committee's view

4.4 Although there have been many scientific developments since the Warnock Committee reported, the basic ethical arguments have not changed substantially since then. Positions range from those taken by pro-life groups and some of the churches that the early embryo is a human being in the fullest sense from the moment of fertilisation and should be accorded the same respect as a human foetus or baby, to the position that, because at the earliest stage of its development the embryo is no more than a collection of undifferentiated cells, albeit with the potential to develop into a human being, it deserves little more attention than any other isolated human cell or tissue.

4.5 The Warnock Committee adopted a position between these opposing views, concluding that the early embryo has a special status but not one that justifies its being accorded absolute protection. That view was enshrined in the 1990 Act.

Should the early embryo be treated as a person?

4.6 The debate centres on the concept of respect for persons. Most people accept the idea that persons should be respected, although they may mean various things by this claim; and it is commonly agreed that babies, children and adults are persons. Many believe that the foetus is a person. The main area of disagreement is whether the early embryo is, or should be treated as if it is, a person.

4.7 One common claim about respect for persons is that it demands that we do not treat others merely as means, and in particular that we do not undercut or bypass their capacities to act. Where capacities to act are lacking—for example in infants—similar forms of respect are extended. However, the basic arguments for respect are focused on *persons* thought of in the ordinary way as beings able to think, act and communicate.

4.8 For those who take the view that the early human embryo has all the rights of a person, it follows logically that it is owed full respect and that no research which has the effect of destroying the embryo is permissible.

4.9 Many of the arguments advanced by those who hold this position are theological (see paragraphs 4.18–4.19). However, two arguments are more widely put forward. The first advances the view that, as the early embryo has the potential to become a person, it enjoys the full rights of a human being and should be accorded the respect owed to a human being. The second argument contends that since the embryo is alive it has a right to life.

4.10 Those who deny the force of the potentiality argument argue that the fact that a person has the potential to qualify as a member of some class in the future, if certain conditions are met, does not confer the rights that belong to members of that class of being until those conditions are met. A medical student is a potential physician, and if he or she qualifies may practise as such; but the potentiality alone does not confer a right to practise. A child is a potential voter but has no claim to be treated as a voter until reaching the age of 18.

4.11 Claims that the embryo is a person from the moment of fertilisation are hard to reconcile with standard views of human and personal identity. Although a baby's mental capacity is undeveloped, there is a continuity of identity between the baby and the adult it will become. So we say, looking at a photograph, "That was me as a baby". When it comes to the undifferentiated cells of the blastocyst, however, such a continuity of identity is less

plausible. Those cells also form the placenta and umbilical cord. Furthermore, they can divide to form identical twins. Because there is not the same continuity of identity it is more natural to refer to these undifferentiated cells as a potential person rather than as a person.

4.12 Some would see this view as underpinned by embryological evidence. Although the fertilised egg and blastocyst contain all the genetic signals required for human life, this is true of nearly all cells in the body. However, genetic elements are not sufficient and there is no automatic programme of development from blastocyst to birth. Although the early embryo contains within it the full genetic potential of any person(s) who may develop from it, it requires many other factors, particularly those provided by the maternal environment in the womb, to enable it to realise that potential.

4.13 A gradualist view of the development of the embryo is also seen as consistent with the way cultures react to early embryo loss. Although would-be parents may feel sad at the natural loss of early embryos before implantation, there is no public mourning ritual associated with it, nor is there for the loss of surplus embryos left over from IVF treatment.

4.14 The argument that because the embryo is alive it has a right to life has little weight unless linked to the potentiality argument. The fact that a cell or piece of human tissue is alive is not in itself a reason for according it a full right to life. The claim that an embryo has a full right to life assumes not merely that it is alive, but that it has a status that most living tissue does not have—the very point that has to be established if the embryo is to have a right to life.

4.15 Some of those who ascribe full rights to the early embryo argue that, even if it has not been demonstrated that the early embryo is a person, equally it has not been demonstrated that it is *not* a person. They suggest that early embryos should therefore be given the "benefit of the doubt": even if they are not persons they should be treated *as if* they were persons, and accorded the full rights that we accord to persons.

4.16 Burden of proof arguments are notoriously hard to resolve. If there were no morally serious reasons for undertaking research on human embryos, then the mere possibility that the early embryo is a person would be sufficient reason not to do such research. However, if there are morally weighty reasons for doing such research a decision must be reached on the basis of arguments that fall short of proof.

4.17 There are morally weighty reasons for doing research that may lead to therapies for many serious and common diseases, and the concept of respect for persons can also be invoked on this side of the argument. A commitment to respect for persons is fundamental to many areas of life, not least the practice of medicine, in which help and assistance to those in need is a guiding principle. Here respect for persons may take the form of developing treatments for serious degenerative diseases, and there can be few causes more worthwhile than to relieve the suffering caused by these diseases. We received a good deal of evidence from people suffering from such diseases, particularly Parkinson's disease, which illustrated this. It would be wrong not to seek therapies for such diseases, which necessarily involves undertaking the fundamental research that may make those therapies possible. Unless early embryos have an unconditional claim to protection, therefore, it would be wrong to rule out research involving them for such a purpose.

The views of the faiths

4.18 The various positions set out in the previous section are also found in the teaching of religious bodies. On the one hand, there are those that teach that the early embryo must be fully protected from the moment of conception. On the other hand, there are those that take a gradualist position. And there are differences of view and emphasis within many of these religious traditions. Amongst those that take an absolutist view of the status of the early embryo and the protection to be accorded to it, the Roman Catholic Church is opposed in principle to any destructive interference with the early embryo. The Catholic Catechism states that, "Human life must be respected and protected absolutely from the moment of

conception".[29] The basis of this view is that either the early embryo is a person or, even if it may not be, as long as there is not total certainty that it is *not* a person, it must be given the benefit of the doubt and treated as if it were. This view is shared by some other Christians. It was also put to us as the Muslim view by the Islamic Medical Association, "He/she should be fully respected from the moment of conception and the fertilised egg is a sacred being" (p). We understand that the Hindu view is similar, reflecting the fact that traditional Hindu thought regards abortion as a major transgression.[30]

4.19 Some other Christian Churches interpret the Christian tradition differently from the Roman Catholic Church.[31] They take the view that the early embryo is not yet a person and that its potential to become one does not give it a claim to be treated as a person. On this reading of the Christian tradition the respect to be accorded to an early embryo is not absolute from the moment of fertilisation but develops as the embryo develops. Thus in giving evidence with the Board for Social Responsibility of the Church of England the Bishop of Rochester referred to "taking a developmental view of the emergence of personhood" (Q160). The evidence we received from the Court of the Chief Rabbi stating the Jewish position also put forward a gradualist position:

> In Jewish law neither the foetus nor the pre-implanted embryo is a person; it is, however, human life and must be accorded the respect due to human life. Personhood, with its attendant rights and responsibilities begins at birth. Prior to birth, we have duties to both the embryo and the foetus, but these may, in certain circumstances, be overridden by other duties, namely those we owe to persons (p 60).

The current legal and social context

4.20 The debate on the moral status of the early embryo will no doubt continue. Members of the Committee have different views of the strength of the arguments set out above. But, whatever those individual views, the Committee believes that the question of research on human embryos has to be considered within the context of the law in the United Kingdom and the social attitudes it reflects. There are three main elements to this:

(a) Legislation permitting abortion in a relatively wide range of circumstances has now been in place for over 30 years. In setting an upper limit of 24 weeks for terminations, the Abortion Act, like abortion legislation in many other countries, reflects a gradation in the respect accorded to a foetus as it develops from the early embryo to its birth.[32] This is, of course, not a consideration that is persuasive to those opposed to abortion in all circumstances. But the Act reflects majority public opinion and has been tested on several occasions since it was enacted. It would be difficult to justify an absolute prohibition on the destruction of early embryos while permitting abortion in a relatively wide range of circumstances post-implantation—indeed well after the emergence of the primitive streak and into the foetal stage of development.

(b) IVF has been used to assist reproduction for 25 years and has a wide measure of public support. As currently practised, it necessarily results in the creation of a substantial number of surplus embryos, most of which are eventually destroyed. To accord the early embryo the full protection accorded to a person would also be inconsistent with the use of IVF.

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[29] Paragraph 2270.

[30] The Bahá'í view is, similarly, "that any cell, group of cells or embryo having the potential to develop into a separate individual is sacred and has a soul." (Memorandum by Bahá'í Community of the United Kingdom (p 227)).

[31] The different interpretations of the Christian tradition are described in Appendix 4.

[32] The original limit of 28 weeks in the Abortion Act 1967 was reduced to 24 weeks by the 1990 Act (section 37 (1)(a)).

(c) The 1990 Act, which regulates research on human embryos strictly, was enacted after a lengthy period of public and parliamentary debate. It has been in force for ten years and also enjoys a wide measure of public support.

The Committee's conclusion

4.21 **Whilst respecting the deeply held views of those who regard any research involving the destruction of a human embryo as wrong and having weighed the ethical arguments carefully, the Committee is not persuaded, especially in the context of the current law and social attitudes, that all research on early human embryos should be prohibited.**

The fourteen days limit

4.22 If the respect to be accorded to an embryo increases as it develops, this is a gradual process and it may be difficult to establish precisely the point of transition from one stage to the next. The 1990 Act established 14 days as the limit for research on early embryos. Fourteen days has an objective justification insofar as it represents the stage at which the primitive streak, the precursor of the development of a nervous system, begins to appear. This limit seems to have been widely accepted, and the research done under the Act under licence from the HFEA has attracted very little criticism from those who accept the case for research on early embryos. We have received no evidence to suggest that, if research on human embryos is to continue, there should be a different limit. In point of fact the stage at which stem cells need to be extracted for research is very much earlier than that—at the blastocyst stage—when the early embryo is still smaller than a pinhead. **The Committee considers that 14 days should remain the limit for research on early embryos.**

What does respect for the early embryo mean in practice?

4.23 The Warnock Committee recommended that "the embryo of the human species should be afforded some protection in law" but that protection could be waived in certain specific circumstances.[33] Some of our witnesses took issue with the idea of a status that attracted only limited protection, arguing that it was hypocritical to profess respect for something you were going to destroy. It is true that if an embryo had full human rights it would be inconsistent to do anything that had the effect of destroying it. But to maintain a position that falls short of total protection for the embryo does not in our view equate to a total absence of respect.

4.24 Nevertheless there can be confusion about how respect for an embryo should be demonstrated. It may be helpful to try to clarify it. It is sometimes assumed that respect simply means the respectful treatment and disposal of embryonic tissue in the laboratory. This is certainly important, as with any human tissue. The reaction to the removal of organs from children at Alder Hey Hospital shows the importance attached to the physical treatment of human tissue, in that case body parts, even when it is no longer alive.

4.25 When living tissue is involved, a further degree of sensitivity is necessary. The 1990 Act requires this to be demonstrated in the following ways:

(a) through the extensive restrictions that are rightly placed on the use of embryos—the 1990 Act permits research on embryos to be carried out only if there is no alternative available and it is necessary or desirable to achieve one of the permitted purposes;

(b) through strict adherence to the rules governing the informed consent of the donors (we return to this issue in Chapter 8);

(c) through restrictions on export where restrictions on use after export could not be overseen or enforced;

[33] Paragraph 11.17.

(d) through restrictions on mixing with non-human material; and

(e) through meticulous record-keeping of the creation and disposal of early embryos for research so that every embryo is accounted for.

The creation of embryos for research

4.26 At present research on embryos is conducted almost exclusively on embryos created for the purpose of IVF treatment which are surplus to requirements and are donated specifically for research purposes. Between 1 August 1991 and 31 March 1999 53,497 surplus embryos were donated for research.[34] The 1990 Act also permits the creation of embryos for research. This was an issue on which the Warnock Committee was divided. It recommended by only a narrow majority in favour of allowing the creation of embryos for this purpose. Since the Act came into force 118 embryos have been created for research.

4.27 The creation of embryos (whether by IVF or CNR) for research purposes raises difficult issues. Some argue that, if an embryo is destined for destruction, it is more honest to create it specifically for the purpose of research than to use one created for reproductive purposes. But most of those who commented on this issue regarded it as preferable to use surplus embryos than to create them specifically for research. They took the view that an embryo created for research was quite clearly being used as a means to an end, with no prospect of implantation, whereas at the time of creation the surplus embryo had a prospect of implantation, even if, once not selected for implantation (or freezing), it would have to be destroyed. We agree that for this reason it is preferable to use surplus embryos for research purposes if the same results can be achieved with them. It is currently unavoidable that there should be some surplus embryos from IVF treatment, although desirable that the numbers should be reduced as more effective techniques are developed.

4.28 There may, however, be some research needs for embryos that cannot be met by the use of surplus embryos, for example when the research is concerned with the act of fertilisation itself. Two examples of such research that were licensed by the HFEA are: to test techniques of freezing eggs, which are very fragile, in order to assess the normality of an embryo created from an egg that has been thawed and fertilised; and the development of Intra-Cytoplasmic Sperm Injection. This procedure involves the direct injection of a sperm into an egg as a means of securing fertilisation by immature sperm. It was necessary to create an embryo to test the effectiveness of the technique and demonstrate its safety.[35] The very small number of embryos created over the last ten years suggests that in practice there is little demand to create embryos by IVF for research. **The Committee believes that embryos should not be created specifically for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos.**

[34] HFEA, *Ninth Annual Report and Accounts*, 2000. More up to date figures are not yet available.

[35] Q 7.

CHAPTER 5: CELL NUCLEAR REPLACEMENT AND CLONING

The additional purposes in the Regulations

5.1 As described in Chapter 1, the 2001 Regulations extend the purposes for which research on early embryos may be undertaken from purposes connected with reproduction and treating infertility to certain purposes concerned with understanding the development of the embryo and increasing knowledge of, and developing treatments for, serious disease. The possibility of an extension was foreshadowed in the 1990 Act, which provides (in Schedule 2) for the original purposes to be extended by regulation.

5.2 In the debates on the Regulations one of the issues on which there was disagreement was whether the change effected by them was a matter of degree or such a substantial change that, as some argued, it should have been introduced by fresh primary legislation.

5.3 We asked all our witnesses if they saw the additional purposes as raising new issues of principle. Some—mostly (but not exclusively) those opposed to research of any kind on early embryos—contended that new issues of principle did arise, in so far as the original purposes were strictly limited to reproductive research, while the new purposes were much more widely drawn. In their view the purpose of understanding the development of the embryo entailed basic research rather than research directed at specified desirable objectives. The All-Party Parliamentary Pro-life Group, for example, argued that "the regulations allow 'pure' research on human embryos, without reference to clinical goals, for the first time" (p 213). In his memorandum Lord Habgood said: "they [the Regulations] are much too open-ended and are thus in danger of destroying the broad ethical consensus on which the original regulations are based" (p 390). It was also argued that under the Regulations the embryo would be used instrumentally, as a means to an end, whereas under the original purposes, the research, although it could not benefit the embryo that was the subject of it, was at least intended to benefit the class of embryos as a whole by improving reproductive techniques. On the other hand, the view was also put to us by the Society for the Protection of Unborn Children that there was no difference in principle because all destructive research on embryos is unethical (p 111).

5.4 The majority of our witnesses, however, did not see the additional purposes as raising new issues of principle. They regarded treating serious disease as at least as worthwhile as promoting advances in the treatment of infertility, and we find that a persuasive argument. In our view it is difficult to maintain that the embryo is being used instrumentally under the new purposes but not under the original purposes, one of which is developing more effective techniques of contraception, which can hardly be said to benefit the class of embryos. We accept that, as we explained in Chapter 2, at least initially, some of the research carried out under the Regulations is likely to be basic research, designed for example to understand the process of cell differentiation. **Basic research is a necessary step to developing treatments and facilitating the potential use of adult stem cells and should be permitted under the Regulations in the same way as more directly applied research to which it is designed to lead, provided that it is subject to strict regulation.**

Cell nuclear replacement

5.5 If the extension of the purposes had been the only point at issue in the Regulations, it is unlikely that they would have attracted the degree of attention that they did. What underlay anxiety about them was the perception that they would permit the creation of embryos by the technique of CNR—popularly described as cloning. That was seen as objectionable for two main reasons: first, because it would be one way of creating embryos specifically for research or therapeutic purposes; and, secondly, because it would be a step on the slippery slope to "reproductive cloning", that is the production of a baby by implanting the embryo generated by CNR in a woman's uterus and allowing full development. It was also seen as contrary to the spirit of the 1990 Act, section 3 (3)(d) of which prohibits "replacing a nucleus of a cell of

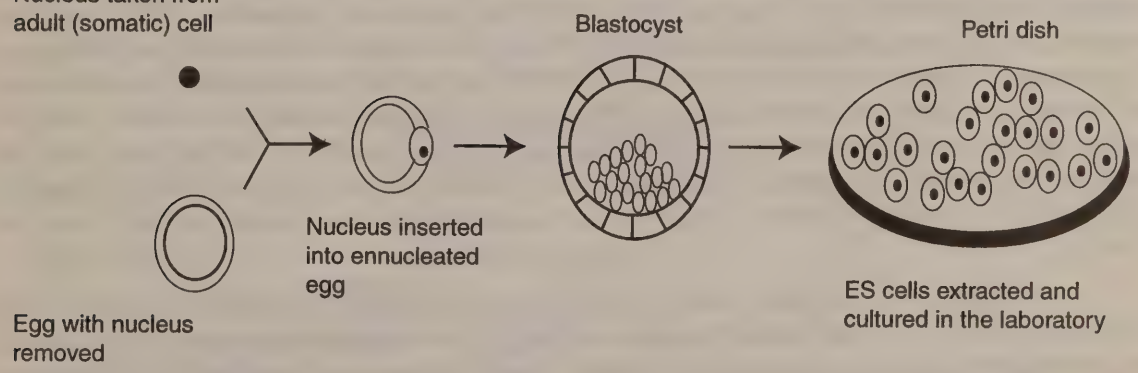
an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo", the only form of cloning known at the time.

5.6 CNR is the process of inserting the nucleus of an adult cell into a donated egg from which the original nucleus has been removed. Following CNR, if the recipient egg is induced to divide, an embryo can be produced. CNR was the first step in the process by which Dolly the sheep was created.

5.7 CNR is, potentially, a way of producing compatible tissues for patients which will not be rejected by their immune systems. It would involve creating a zygote by CNR using a nucleus from an adult cell of the individual to be treated, and growing it to the blastocyst stage. ES cells would be isolated from the blastocyst (which would be destroyed in the process) and differentiated *in vitro* to produce cells or tissue for implantation. The process is illustrated in diagram 1 The use for therapy of ES cells produced in this way has a potential advantage over the use of ES cells isolated from early embryos created by IVF, because the genetic material would be derived from the individual to be treated and so would not be rejected by the host immune system.

Diagram 1 *

Embryonic stem cells from cell nuclear replacement - key steps



*Based on Figure 2 of the Donaldson Group's report (p 23).

5.8 The procedure described in paragraph 5.7 is often referred to as "therapeutic cloning", to reflect the fact that it is envisaged only as a means of generating ES cells for direct application in treatment and therapies: the embryo itself is grown only to the blastocyst stage and is not implanted or allowed to develop further. This is in contrast with "reproductive cloning", in which the blastocyst would be implanted in a woman's uterus with a view to producing a baby. Thus, the distinction between "therapeutic" and "reproductive" cloning is based on the steps following CNR, and reflects the purpose for which it is undertaken. The initial process (to the blastocyst stage) is identical. Under the Human Reproductive Cloning Act 2001 the implantation in a woman of a CNR embryo is now a criminal offence. In this report we refer simply to the technique—cell nuclear replacement—by which a blastocyst is produced by CNR for non-reproductive purposes.

5.9 The majority scientific view presented to the Committee was that for practical reasons CNR is unlikely to provide a general basis for therapies in the foreseeable future. We were

told that individualised treatments using the patient's own cells[36] would be difficult and expensive and would require a continuing supply of human eggs, which is unlikely to be forthcoming on a large scale. Some medical charities and patients' support groups argued that female members of a patient's family would be prepared to donate eggs for altruistic motives, and this is no doubt true in some cases. Opponents of CNR argued that it would be difficult to avoid pressure being brought to bear on potential donors, although that is a problem that has up to now been dealt with successfully in the United Kingdom by strict regulation of gamete donation, including a prohibition on payment. As a response to these problems it has been suggested that CNR might be used to generate a bank of ES cells from which the best "match" with the patient could be selected to minimise the risk of immune rejection. Several thousand ES cell lines generated by this process would be required. Whether this is a realistic possibility remains to be seen.

5.10 However, even if CNR does not become a general basis for therapies in the foreseeable future, it still has significant potential as a research technique since it would provide a powerful approach to studying the process of dedifferentiation. In producing Dolly the sheep CNR has shown that dedifferentiation of adult cells is possible and gave a major impetus to research into that process. The biochemical signals which control the process of dedifferentiation and maintain the genetic material in a pluripotent state are contained in the oocyte (female egg). CNR research at present provides the only realistic means of identifying these factors and establishing how to reverse the signals that "mark" the DNA during differentiation and must be erased during dedifferentiation.

5.11 The Regulations make no direct reference to CNR. The 1990 Act did not specifically prohibit the creation of embryos by CNR—the technique had not been used successfully on mammals at that time, and was not until Dolly the sheep was created in 1996; and the Regulations did not specifically authorise it. When CNR became a practical possibility the Department of Health was of the opinion, on the basis of counsel's advice, that the definition of "embryo" in the Act would include CNR embryos so that research on them—whether under the Act or the Regulations—would be regulated by the HFEA in the same way as research on fertilised embryos. This view has now been upheld by the Court of Appeal (although, as noted in Chapter 1, there is the possibility of a final appeal to the House of Lords).

5.12 No application has been made to the HFEA for a licence to create embryos by CNR for research related to the original purposes in the Act. As long as the purposes were limited to reproductive purposes, there was little reason to seek to create embryos by CNR. However, it is generally accepted that extending the purposes to understanding the causes of (and by implication developing treatments for) serious disease is likely to stimulate applications to do research involving CNR embryos.

5.13 The 1990 Act already allows embryos to be created for research, although as noted in Chapter 3 only 118 have been created for research purposes since the Act came into force. A few of our witnesses drew a distinction between the creation of an embryo (for research) by IVF and by CNR on the ground that the latter represented a further step away from natural means of creating embryos. But the main ground of opposition to the creation of embryos by CNR was that it would increase the likelihood of such embryos being implanted in a woman. We discuss this "slippery slope" argument later in this Chapter. **Although there is a clear distinction between an IVF embryo and an embryo produced by CNR (or other methods) in their method of production, the Committee does not see any ethical difference in their use for research purposes up to the 14 days limit.**

5.14 **The Committee concludes that, even if CNR is not itself used directly for many stem cell-based therapies, there is still a powerful case for its use, subject to strict regulation by the HFEA, as a research tool to enable cell-based therapies to be developed. However, as with embryos created by IVF for research, CNR embryos**

[36] i.e. using CNR to produce cells or tissue genetically identical to the patient's. These considerations would not apply to the same extent if CNR were used to create stem cell lines.

should not be created for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos.

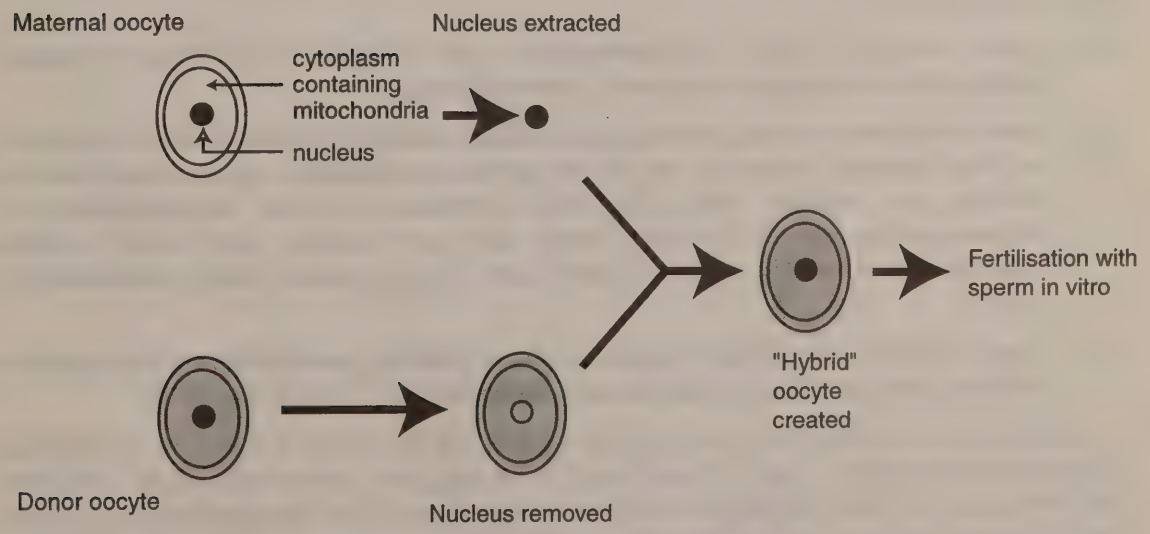
Oocyte nucleus transfer

5.15 Oocyte nucleus transfer, a process akin to CNR, may have the potential for treating mitochondrial diseases. Mitochondria are small energy-producing structures present in every cell. They were described by one of our interlocutors as filling the role of batteries or a power pack. Most of a cell's DNA[37] is contained in the nucleus, but a very small amount (less than one per cent) is found in the mitochondria. Alterations in the mitochondrial DNA result in a number of relatively rare but very serious diseases. Mitochondria are present in the female egg, but are not transferred from the male sperm during fertilisation, so the mitochondria of the embryo are derived exclusively from the mother and mitochondrial diseases are transmitted only through the maternal line.

5.16 If a woman is a carrier of mitochondrial disease, oocyte nucleus transfer might offer the possibility of preventing its transmission to her children. Using this technique, the nucleus would be extracted from the woman's egg and transferred to a donated egg from which the nucleus had been removed. The egg could then be fertilised by IVF and implanted in the mother. The procedure is illustrated in Diagram 2. The resulting embryo would receive the vast majority of its genes from the mother and father in the normal way—it would not be a clone—but the small number of mitochondrial genes would come from a third person, the woman who donated the egg. This is sometimes characterised as the resulting baby having two genetic mothers.[38]

Diagram 2*

Treating mitochondrial disease by
oocyte (egg) nucleus transfer - ket steps



*Based on Figure 3 of the Donaldson Group's report (p 28).

[37] Deoxyribonucleic acid—the cell's and the body's genetic material.

[38] An alternative approach to preventing the transmission of mitochondrial disease would be simply to use a donated egg for fertilisation by the father's sperm, but the resulting embryo would not, of course, then contain any of the mother's genetic material.

5.17 The Donaldson report noted that very little research has been carried out on this procedure, and that it would need extensive testing in animal models, and with human eggs, before it could be used therapeutically in humans. [39]

5.18 It has been suggested that oocyte nucleus transfer would constitute a breach of the prohibition on germ-line gene therapy.[40] Because of the transmission of mitochondrial DNA, the procedure would involve a (relatively small) modification of the human genome.[41] However, this issue does not arise at the research stage, which is the extent of our remit, and should not therefore be a barrier to research.

5.19 A further objection that has been raised is that the procedure would breach the 14 days limit for human embryo research. We do not see that research into oocyte nucleus transfer would breach the 14 days limit any more than it does with CNR. The Human Genetics Advisory Commission and the HFEA concluded in their 1998 Report that CNR would not breach the 14 days limit.[42] They said, "whether the nucleus to be replaced in an enucleated oocyte is taken from an adult or from another embryo, the clock is put back to the beginning, embryonic development starts over again and the primitive streak stage specified in the Act would still not be reached within the 14 day time limit".

5.20 The Regulations with which we are concerned relate only to research. There is no doubt that mitochondrial diseases are serious diseases and oocyte nucleus transfer may have great potential for treating them. There is a strong scientific and medical case for further research into it **and we conclude that if CNR is permitted in certain limited circumstances, oocyte nucleus transfer should also be allowed for research purposes.**

"Reproductive cloning"

5.21 The question of human reproductive cloning is not central to our terms of reference, since it was never envisaged that it would be permitted under the Regulations. However, we have examined the issues surrounding it because of the argument that the use of CNR for research purposes represents a slippery slope to reproductive cloning.

We set out our analysis in more detail in Appendix 6. In summary the Committee's conclusions are that:

(a) **given the high risk of abnormalities, the scientific objections to human reproductive cloning are currently overwhelming;**

(b) **there are further strong ethical objections in addition to those based on the risk of abnormalities, although not all the arguments deployed against reproductive cloning are equally valid. The most powerful are the unacceptability of experimenting on a human being and the familial and child welfare considerations arising from the ambiguity of the cloned child's relationships; and**

(c) **the Commitee unreservedly endorses the legislative prohibition on reproductive cloning now contained in the Human Reproductive Cloning Act 2001.**

5.22 Is there then a risk that allowing the use of CNR for research purposes would make reproductive cloning more likely? In so far as the starting point is the same, there is no doubt that developing the CNR technique would in technical terms facilitate reproductive cloning. But the fact that a technique developed for a worthwhile purpose may be used for different, unacceptable, purposes is not a conclusive argument for prohibiting it. Both the potential

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[39] Paragraph 4.25.

[40] A modification of the human genome in which a person's genetic material (DNA) is altered in the germ cells such that the alteration can be passed to the next generation.

[41] The complete genetic material of an individual.

[42] *Cloning Issues in Reproduction, Science and Medicine*, December 1998.

benefits and disadvantages and the level of risk and possible safeguards need to be taken into account.

5.23 Some pronouncements give the impression that it would be a simple matter to produce a cloned baby. This is far from the case. Apart from the practical problems referred to in Appendix 6, it would require a well-equipped fertility clinic and the services of a number of different specialists. Any clinic participating in this work would lose its licence from the HFEA, and the personnel involved would now be at risk of committing a criminal offence punishable with ten years' imprisonment.

5.24 **The HFEA has an excellent record in ensuring that IVF clinics comply with the law, and we are satisfied that its regulatory powers, now reinforced by a specific statutory prohibition, provide sufficient protection against the development of CNR leading to reproductive cloning in the United Kingdom.**

5.25 The regulatory system in the United Kingdom cannot, of course, prevent attempts to undertake reproductive cloning in other countries. We discuss in Chapter 7 the case for seeking to negotiate an international ban on reproductive cloning.

CHAPTER 6: COMMERCIAL INTERESTS IN STEM CELL RESEARCH

6.1 This report concentrates largely on scientific and ethical issues arising from stem cell research. The Committee has, however, been aware throughout that commercial interests could, and to some extent already do, play an important part in the development of such research. Since we have received only a limited amount of evidence on this aspect of the subject and were unable to probe further within our time constraint, we simply identify the issues which have come to our attention. They are, however, of considerable significance for the legal and regulatory control of stem cell research, in which companies involved in stem cell research have an obvious interest.

6.2 Biotechnology is a growth industry. In their last annual European Life Sciences Report[43] the consultants Ernst & Young reported that by the end of 2000 the total value of Europe's publicly quoted biotechnology companies stood at 75 billion Euros, compared with 36 billion Euros a year earlier. According to a separate report, in the United States which has the largest number of companies in this field, market capitalisation of publicly quoted biotechnology companies fell over the same period (from $353.8 billion to $330.8 billion) but the number of public companies increased by 12.6 per cent, and in the two years to June 2001 biotechnology stocks outperformed internet stocks and the Nasdaq index.[44] Within Europe the United Kingdom has by far the most public biotechnology companies, although there are more private companies in Germany. Investor interest is considerable and evidently based on the assumption that future profits may be significant.

6.3 Only a small number of biotechnology companies engage in stem cell research. Most current work is being undertaken in academic research institutes, supported in the United Kingdom by government funding through the Research Councils and by the Wellcome Trust.[45] However, some work is done by the large pharmaceutical firms, even though it is not entirely clear at this stage what form the commercial applications may take, given that stem cell therapy will be a form of treatment rather than a drug-based therapy. Sir Richard Sykes, the Chairman of GlaxoSmithKline, in his evidence stressed the interest of these companies in fundamental research, even if applications are still uncertain. He identified three main areas where he saw the biopharmaceutical industry benefiting commercially from stem cell research: in producing new therapeutic and diagnostic agents; in developing standard stem cell lines; and in testing biopharmaceuticals (Q 409).

6.4 Of companies active in stem cell research, the Geron Corporation in the United States is widely regarded as a world leader. In the United Kingdom, the Celltech Group, which features in the FTSE 100 Index, conducts research in this area. The best known company in the United Kingdom in this field is probably PPL Therapeutics, the commercial arm of the Roslin Institute, which created Dolly the sheep. PPL Therapeutics is associated with the Geron Corporation. More recently, in November 2001, the American biotechnology firm Advanced Cell Technology (ACT) made headlines with the claim to have created a human embryo by CNR. (Similar claims were made by researchers in Seoul, South Korea in 1998.) Some regard such claims as public relations stunts in the competition for investors.

6.5 China—and in other ways Singapore—provide examples which deserve special mention. In China the government has encouraged a number of universities to invest heavily in stem cell research. In doing so universities have attracted not only public funds but investment by private companies like the Beijing Stemcell Medengineering Company. Leading Chinese researchers are often US-trained and have links with American laboratories. In Singapore, the Economic Development Board has provided initial finance for the Singapore Genomics Programme; it is said that by 2005 some $7 billion dollars will have been invested in relevant research. In both China and Singapore there is concern with ethical issues but also an interest to maintain the competitive advantage gained by light regulation.

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[43] *Integration*, Ernst and Young's Eighth Annual Life Sciences Report, 2001.

[44] *Focus on Fundamentals; The Biotechnology Report, 2001.*

[45] The current level of funding was given in paragraph 2.7.

6.6 It is not easy to gather solid data on trade in stem cells or stem cell lines. So far as research under present regulations in the United Kingdom is concerned, it appears that exchange of cell material takes place on a non-commercial basis between individual scientists or research units. However, there may be a less visible trade. It is unlikely that official figures of available stem cell lines give the whole picture.

6.7 Particular issues of both commercial and scientific significance arise from the patenting of research findings and stem cell lines. Not surprisingly, American firms—or lawyers—have been particularly effective in securing patents which make it costly for others to pursue certain lines of research. The Geron Corporation is said to be the leading owner of patents based on stem cell research.

6.8 The Nuffield Council on Bioethics has warned against the granting of over generous patents in the United Kingdom.[46] In his evidence to us Sir Richard Sykes took a more relaxed view. Pointing out that the broader the patent the more susceptible it would be to attack, he told us that he was satisfied that the present system maintained a reasonable balance between protecting the intellectual property rights of inventors and not stifling research (Q 412). We see the force in this argument. But patent litigation is expensive and only a major player is likely to have the resources to attack a patent held by a major biotechnology company. For a smaller player the economically rational decision may be simply to pay the licence fee. We share the concern expressed by the Nuffield Council that the technologies to produce and make use of stem cells should not be restricted by overly broad patents. We are not in a position to make a firm recommendation on this issue but it is clearly a matter that needs to be kept under review to ensure that there is a fair balance between the needs of research and the rights of patent-holders.

6.9 The Committee has drawn only tentative conclusions from this admittedly sketchy picture. Biotechnology is a growth area of business, and stem cell research plays a part in its development. Although considerable sums are available for investment in it, commercial returns on such investment are for the moment at best modest. Even the Geron Corporation appears to have made a loss in the field of stem cell research in 2001. This reflects the fact that most of this work is still at the basic research stage. Thus commercial interests are trying to position themselves for major profits in the future, but still face uncertain research prospects let alone uncertain therapeutic possibilities.

6.10 The regulatory regime for research on early human embryos needs to be based—as it has been in the United Kingdom—on careful assessment of the ethical, social and scientific considerations without regard to future commercial benefits. But, subject to that regulatory regime, commercial interests will have a key role to play in developing therapies and in bringing effective treatments to patients as quickly as possible, and they should be encouraged. In the United Kingdom there has been a fruitful collaboration between industry and research institutes and we strongly endorse the need for this to continue.

[46] *Stem cell therapy: the ethical issues,* Nuffield Council on Bioethics, London 2000, p 12.

CHAPTER 7: THE INTERNATIONAL DIMENSION

7.1 Stem cell research and cloning are not purely domestic issues. Scientific research and its commercial exploitation operate on a global basis: both are sensitive to differences in the regulatory environment.

7.2 Some aspects of stem cell research and cloning are covered by international instruments and other declarations; and some commentators take the view that there should be a greater degree of international regulation in this field. The issues that we have been considering have arisen in similar form in other countries and in formulating our views we have sought to take account of their experience.

International instruments: the concept of human dignity

7.3 Most of the relevant provisions of international instruments in this field are concerned with reproductive cloning rather than research on human embryos.[47] However, Article 18 of the Council of Europe Convention on Human Rights and Biomedicine states categorically that "the creation of human embryos for research purposes is prohibited". The United Kingdom has not signed this Convention.

7.4 The European Parliament has also taken a close interest in the subject. On 7 September 2000 it passed a resolution on human cloning in reaction to the new Regulations brought forward by the British Government.[48] The resolution emphasised the need to respect human dignity and human life, called on the United Kingdom Government to review its position on human embryo cloning and repeated calls for each Member State to enact binding legislation prohibiting all research into human cloning and to provide for criminal penalties. The Parliament subsequently set up a Temporary Committee on Human Genetics and Other New Technologies of Modern Medicine; we were able to meet some of its members when they visited the United Kingdom. The Temporary Committee reported on 8 November 2001.[49] The report itself recommended a cautious approach to stem cell research and raised a number of questions. It recognised that decisions would probably—and rightly—continue to be taken at Member State level, whereas the EU would decide where and how it should direct its research and funding priorities. The draft resolution proposed for adoption by the Parliament, however, was in uncompromising terms, calling in effect for a ban on all research on human embryos and embryonic stem cells.

7.5 When the report was debated on 29 November 2001, the Parliament voted by 316 to 37 (with 47 abstentions) to reject the final motion for a resolution after amendments in favour of "therapeutic cloning" were earlier approved.

7.6 In instruments such as the European Convention, as in much modern bioethical thinking, the starting point for regulation is taken to be the principle of respect for human dignity. A secular principle of respect for human dignity goes back to the Enlightenment and is closely linked to the development of claims about human rights. On one view human dignity is seen as synonymous with human worth and is said to form the basis of human rights. On another view it is specifically associated with particular human rights, such as

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[47] The UNESCO Universal Declaration on the Human Genome And Human Rights states that "practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted"; Article 1 of the Additional Protocol to the Council of Europe Convention on Human Rights and Biomedicine provides that "any intervention seeking to create a human being genetically identical to another human being whether living or dead is prohibited"; and Article 3 (2) of the Charter of Fundamental Rights of the European Union states that the prohibition of the reproductive cloning of human beings must be respected. There is no directly relevant provision in the European Convention on Human Rights. Some have argued that restrictions on reproductive technology could violate the right to respect for private and family life contained in Article 8 (1) but no one has yet sought to test this proposition.

[48] B5-0710.

[49] PE 300.127.

those concerned with the basic conditions for working people. More recently the concept of human dignity has been invoked by those opposed to certain biomedical developments, notably cloning.

7.7 The concept of human dignity raises interesting philosophical issues, but has proved hard to analyse.[50] We have not been able to derive much practical guidance from recent claims about human dignity as to what should and should not be permitted in the field of research on human embryos. One reason for this is that most people can agree that persons should be treated as having dignity and not be used as mere means; but mere reiteration of this point with respect to early embryos begs the question of whether they count as persons, which we discussed in Chapter 4.

National differences

7.8 The differences in attitudes to stem cell research between different countries and in its regulation are striking. As many of our witnesses testified, these differences largely reflect differences in cultural and religious traditions. We have sought to inform ourselves about international developments, but legal and regulatory regimes are changing so rapidly in many countries that we have not attempted to produce a comprehensive account of the situation in other countries.

7.9 In the countries of the European Union, a variety of regulatory regimes for research on early embryos are currently in operation, though in this regard too the scene is rapidly changing. Reproductive cloning is either illegal or in practice prohibited everywhere. In several countries there is currently no legislation governing stem cell research. Sweden and the Netherlands (along with the United Kingdom) are generally regarded as having the most "liberal" rules. In December 2001, the Swedish Research Council issued guidelines endorsing the use of CNR (but not of the creation of embryos by IVF for research) subject to certain conditions, including legislation to prohibit placing such embryos in a woman. In the Netherlands the Parliament passed a law in October 2001 allowing research on surplus embryos; and allowing CNR after a moratorium of five years. At the other end of the scale, embryo research is banned in Ireland and in Germany. However, in Germany the *Bundestag* decided on 30 January 2002 (by a free vote of 339 to 265) to call for legislation permitting the import for research of stem cell lines which were established before 2 January 2002. In most other countries research using surplus embryos is permitted. Where there are rules they limit permissible research to early embryos up to 14 (in the Netherlands 15) days. A considerable variety of governmental or quasi-governmental agencies have been created to oversee and in some cases license such research.

7.10 The United Kingdom goes further than most countries in permitting the creation of embryos for research and the use of CNR. But it is worth noting that, as many overseas commentators acknowledge, the United Kingdom's position has been reached only after a period of lengthy debate going back over fifteen years and a system of effective regulation that has been in place for over ten years and has been widely admired and used as a model in other countries. The debates currently taking place in other European countries seem to indicate, broadly speaking, movement away from a total prohibition on embryonic stem cell research.

7.11 The situation in the United States has attracted a great deal of attention, partly because some of the ground-breaking work in ES cell research has been undertaken there and partly because of the publicity that attended President Bush's decision in August 2001 to permit federal funding of research on human embryonic stem cells, but only if they were derived from stem cell lines established before 9 August 2001. The rationale of this decision was that there should be no federal support for research involving the destruction of human embryos but that, if the embryo had already been destroyed, the status it previously enjoyed

[50] Professor John Harris has described it, more unequivocally, as "comprehensively vague" (John Harris, *Clones, Genes and Immortality* (Oxford: OUP, 1998) p.31.)

no longer attached to the stem cells extracted from it. President Bush's announcement referred to some 60 such stem cell lines throughout the world (none of them generated in the United Kingdom).[51] This decision reflected the fact that the main control that the federal government exercises on human embryo research is through its funding of research. There is no federal control of privately funded research, which is generally subject to State rather than federal regulation. This has led to significant variations between the States. In some States research on human embryonic stem cells is prohibited altogether, in others there is no regulation and therefore little control on what takes place in private research facilities.

7.12 A Bill to prohibit all forms of cloning which has the support of President Bush was passed by the House of Representatives in July 2001 but has not as yet been scheduled for debate in the Senate.

7.13 In Australia, the House of Representatives Standing Committee on Legal and Constitutional Affairs recently completed a two-year long inquiry into a national approach to regulations for stem cell research and cloning. Its report, recommended, among other things, a ban on the creation of embryos (by IVF) solely for research purposes; allowing the extraction of stem cells from spare IVF embryos; a ban on reproductive cloning; and a three year moratorium on the use of CNR.[52]

The scope for international regulation

7.14 Apart from the Council of Europe Convention on Human Rights and Biomedicine, which specifically prohibits human reproductive cloning and the creation of human embryos for research, most of the international instruments have been in fairly broad declaratory terms. We have considered whether there is scope for a greater measure of international regulation in this area. Some witnesses argued that there was a need for such regulation because of the ease with which research and treatment facilities can be transferred to countries with more favourable regulatory regimes, thus encouraging what is sometimes termed "reproductive tourism". On the other hand, a number of scientific witnesses argued strongly that reputable scientists do not look for a research environment with minimum regulation but want an effective regulatory regime which sets out clearly what is and what is not permitted, so that they know where they stand both scientifically and ethically; and that is why the regulatory environment in the United Kingdom is attractive to researchers.

7.15 In our view, any attempt at detailed regulation at international level, even if theoretically desirable, would inevitably founder on the wide differences in policy and practice which we have described above. A number of witnesses put it to us that the United Kingdom should be advocating the principles of the 1990 Act and the regulatory regime operated by the HFEA as the basis of international regulation. But that too, it seems to us, would probably be impractical.

An international ban on reproductive cloning?

7.16 It has been suggested that at the very least there should be an international ban on human reproductive cloning, and the Government have indicated that they would support one.[53] Others, notably the Royal Society, have called for a moratorium rather than an outright ban.

7.17 Securing international agreement is never easy, whatever the field of activity, and there would no doubt be formidable practical difficulties in negotiating a ban (or moratorium)

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[51] There has been some dispute about the accuracy of this figure as many have not been documented in detail.

[52] *Human cloning: scientific, ethical and regulatory aspects of human cloning and stem cell research,* Canberra, August 2001.

[53] Lord Hunt of Kings Heath in the debate on the Human Reproductive Cloning Bill, 26 November 2001, Col 58.

even on such an apparently straightforward issue, on which there is known to be widespread agreement.

7.18 Nevertheless, despite the difficulties, we believe that there would be advantage in seeking to secure international agreement on prohibiting reproductive cloning. It would send a powerful signal of international opposition to the practice; it would put moral pressure on countries not to permit facilities in their jurisdictions to be used for this purpose; and it would afford further reassurance to the public that there was protection against the use of CNR for research purposes becoming a slippery slope to reproductive cloning.

7.19 We have not examined in detail what would be the most appropriate international body to negotiate such an agreement, but it should be a world-wide rather than a regional body, which points to the United Nations. The enforcement of an agreement, which might take the form of a Convention, would be the responsibility of the States party to it.

7.20 We have also considered whether action might be taken internationally through professional medical bodies by exerting pressure on scientists and medical practitioners not to attempt reproductive cloning of humans. Such bodies exercise considerable control and influence over their members and it is desirable that they should make their position clear, even if this is unlikely to deter the most determined maverick doctors. However, we do not see professional codes as a substitute for a formal prohibition.

7.21 As mentioned above, the Royal Society has suggested a moratorium rather than an outright ban. The rationale for a moratorium is that it would allow time for all the issues to be explored in detail so that if the scientific objections were overcome, a fresh look could be taken at the acceptability of the practice. We understand the thinking behind this proposal but in our view a moratorium would weaken the moral and presentational effect of an outright prohibition, because it would suggest that there was uncertainty about the ethical objections to reproductive cloning. In addition, the time taken to negotiate a moratorium would be likely to be disproportionate to its length. An alternative might be for any prohibition to have a review procedure built in to it. That would not suffer from the disadvantages of a moratorium to the same extent but would still be weaker than an outright ban.

Conclusion

7.22 **The Committee recommends that the Government should take an active part in any move to negotiate an international ban on human reproductive cloning.**

CHAPTER 8: LEGISLATION AND REGULATION

The existing regulatory regime

8.1 The regulatory system established by the 1990 Act has worked well. The lynchpin of the system is the HFEA. Its work is highly regarded, both at home and abroad. It appeared from the evidence we received that it has the full confidence of the scientific and medical research community, and we believe that it has also been instrumental in reassuring the public that regulation in a particularly emotive area of public policy is carried out effectively and sensitively. It is striking that there have been few legal challenges to the HFEA's rulings and that media criticism has often been on the ground that the Authority is too strict rather than too lax.

8.2 Those opposed in principle to the 1990 Act are understandably unsympathetic to the work of the HFEA, and a few of our witnesses commented on aspects of its work which are outside our terms of reference. Within the field of research on early embryos we received no evidence of any instance where the HFEA's handling of applications under the Act had been the subject of criticism. Some witnesses expressed the fear that, in reviewing applications for research on embryonic stem cells, insufficient attention would be paid to alternatives using adult stem cells (or animals). One witness drew attention to the risk of research applications being peer-reviewed by experts sympathetic to the methodology proposed.[54] We have not received any evidence to support this criticism. The HFEA uses the most distinguished people in the field, from other countries if necessary, to peer-review applications and it is very conscious of its statutory duty to be satisfied that any proposed use of embryos is necessary for the purposes of the research, and that they cannot be achieved by other means.[55] Its approach has not been subject to legal challenge.

8.3 Nevertheless, as the HFEA is very well aware, the 2001 Regulations require it to take a view of areas of scientific enquiry that it did not previously need to consider. The purposes in the 1990 Act are all related, one way or another, to reproductive medicine, whereas applications under the Regulations will be for research relevant to a range of serious diseases and for fundamental research that underlies it. In its evidence to us the HFEA fully recognised the need to call upon a much wider range of experts to advise it on applications under the Regulations.

8.4 As explained in Chapter 2, developments in research on adult stem cells have been proceeding at a great pace. It is possible that at some stage in the future research on adult stem cells will make further research on ES cells unnecessary. It is therefore important that the HFEA also keeps these developments under continuous review. The 1990 Act provides an in-built legislative brake on research on human embryos, since each proposal must be reviewed to ensure that the same results could not be achieved by other research, including research on animals or on adult stem cells. However, we believe that, in addition to this safeguard, a more strategic examination of the potential of adult stem cells is required in the not too distant future. **At an appropriate time, perhaps towards the end of the decade, the Government should undertake a further review of scientific developments, particularly of the progress of adult stem cell research and therapies, and of the development of stem cell banks, with a view to determining whether research on human embryos is still necessary.**

8.5 The Regulations have the potential to extend the HFEA's area of responsibility quite substantially. To maintain its effective regulation of research on human embryos, and to maintain public confidence, it is essential that it should be properly resourced for these additional functions. It is too early to judge the effect of the Regulations on the HFEA's future workload (so far only two applications have been made under them). **But the**

[54] Dr Helen Watt (Q 213).

[55] Paragraph 3 (b) of Schedule 2 to the Act.

Government should keep the funding of the HFEA under review and ensure that it is commensurate with its increased responsibilities.

Review of outcomes of research undertaken under the 1990 Act

8.6 The existing regulatory regime works well in ensuring that applications for licences are carefully considered against the requirements of the Act and that researchers comply with the conditions of their licences. That is, rightly, its main focus. But it is also important to assess whether the research achieves its objectives and realises the benefits claimed for it in the licence application. We believe that there should be a greater focus on outcomes. The public is entitled to know whether the claims made for human embryo research have been realised. The HFEA is probably best placed to undertake a review of this kind since it will have approved the original licence applications and can best judge whether they achieved the purposes in the Act and the Regulations. **We invite the HFEA and the Department of Health to consider how a review of the outcomes of research licensed under the Act might be undertaken and updated on a regular basis.**

The drafting of the Regulations

"Serious disease"

8.7 We looked at two aspects of the drafting of the Regulations in some detail. The first was the use of the term "serious disease". The 1990 Act itself refers to increasing knowledge of disease, without qualification. It was clear from the debates on the Regulations that Ministers expected the HFEA to adopt a common-sense approach, but they only offered very general guidance by reference to examples of diseases that they would regard as serious.

8.8 "Serious disease" is not a term that is defined in other statutes (although in other contexts there are references to "serious disability") and we believe that it would be helpful to have a clearer indication of what it is intended to cover. It is uncertain whether it means serious for the individual or serious for society (the debates suggested that Ministers had the former in mind); and whether it is wide enough to encompass serious injury (to the spinal cord, for example) as well as disease. Moreover, if research properly directed at serious disease later proves to have a useful secondary application for "non-serious" disease, that application should not be ruled out by the fact that the initial research must be relevant to serious disease. We accept that an exhaustive list of serious diseases would be difficult to frame satisfactorily and might involve making invidious distinctions. It would be less difficult to include in the Regulations an indicative list which gave some central examples while making clear that it was not exhaustive. A further possibility would be for the Department of Health or the HFEA to issue non-statutory guidance on the matter. We consider that this last possibility would be the most flexible and would meet the need best. **We invite the Department of Health to examine with the HFEA the possibility of drawing up indicative guidance as to what constitutes serious disease for the purposes of the Regulations.**

Application of the new purposes to basic research

8.9 Secondly, it was suggested to the Committee by several witnesses that the Regulations are *ultra vires* the 1990 Act. On the face of it this is a puzzling suggestion because the Regulations reproduce almost verbatim the terms of the principal enabling provision in the 1990 Act, and this claim was not pursued in the judicial review. However, we did look at the drafting of the Regulations in the light of the way the 1990 Act is framed and the current focus of stem cell research.

8.10 ES cell research and CNR were not in prospect when the Act was passed and we have considered how applications to undertake them would relate to the purposes in the Regulations (the wording of which, as mentioned above, follows closely the terms of the Act). As described in Chapter 2, work on stem cells is at a very early stage and a good deal of

basic research is required before the stage of more applied research is reached. Whilst it may be possible to justify basic research as (eventually) leading to a treatment for serious disease, it is not altogether clear how such research is to be connected strictly to the new purposes. For example, if research is directed at increasing understanding of how cells behave and, in particular, of the mechanisms by which they differentiate and dedifferentiate, it is not immediately obvious how this increases knowledge about the development of embryos, or about serious disease, or about the application of such knowledge to the development of treatments.

8.11 We asked the HFEA how it proposed to consider such applications. The Authority told us that it had received counsel's opinion to the effect that, where an application is directed at understanding how human stem cells behave and differentiate, such research "may be appropriately described" as being concerned with increasing knowledge about the development of the embryo (purpose (a) in the Regulations). In the same opinion, the Authority has been advised that, where such basic research moves beyond purpose (a), consideration will need to be given to whether it falls under purpose (b) (increasing knowledge about serious disease) or (c) (development of treatments for serious disease). Further, counsel has advised that, whilst purpose (b) is confined to "research that may reasonably be anticipated to advance knowledge of the [serious] disease, not the treatment of the disease", purpose (c) may be relevant because it allows for research to be licensed where the purpose is to apply knowledge about the development of embryos with a view to developing treatments for serious disease. On this reading of the Regulations basic research on human embryonic stem cells might be authorised initially under purpose (a), with further applications being subsequently made under purpose (c) when understanding of cell differentiation has reached a point at which treatments for serious disease might be developed.

8.12 An alternative approach, permitting the language of the Regulations to take account of the background legislative purpose (underlying the 1990 Act and the 2001 Regulations), might be encouraged by the Master of the Rolls' judgment in the Pro-Life Alliance case.[56]

8.13 In that case the Master of the Rolls' approach to statutory interpretation draws on guidance given by Lord Wilberforce in *Royal College of Nursing of the United Kingdom v Department of Health and Social Security*.[57] Lord Wilberforce addressed the question of how far the courts can go in judging that new developments (concerning prostaglandin induction methods of carrying out abortions) fall within Parliament's intention (in the Abortion Act 1967). According to Lord Wilberforce, new developments may be held to come within the legislative intention "if they fall within the same genus of facts as those to which the expressed policy has been formulated…[or] if there can be detected a clear purpose in the legislation which can only be fulfilled if the extension is made."[58] However, he emphasised that these principles are to be applied in a way that is sensitive to the legislative context:

> "How liberally these principles may be applied must depend upon the nature of the enactment, and the strictness or otherwise of the words in which it has been expressed. The courts should be less willing to extend expressed meanings if it is clear that he Act in question was designed to be restrictive or circumscribed in its operation rather than liberal or permissive."[59]

He made it clear, however, that gap-filling as such is strictly prohibited:

> In any event there is one course which the courts cannot take, under the law of this country; they cannot fill gaps, they cannot by asking the question 'What would Parliament have done in this current case—not being one in contemplation—if the facts had been

[56] *R (Quintavalle) v Secretary of State for Health* [2002] EWCA, 18 January 2002.

[57] [1981] AC 800.

[58] [1981] AC 800, 822.

[59] Ibid.

before it?' attempt themselves to supply the answer, if the answer is not to be found in the terms of the Act itself.[60]

Significantly, having laid down these guidelines, Lord Wilberforce judged that the extension to the Abortion Act argued for by the Department involved a radical reconstruction of the legislation and was a matter calling for Parliamentary rather than judicial attention.[61]

8.14 Applying Lord Wilberforce's principle in the present context, the key question would be whether the legislative policy was judged to encompass basic research on human embryos (at any rate, where such research is a necessary precursor to the development of therapies for serious diseases). If the legislative purpose were to be so judged, then it would not matter that the particular line of research (involving ES cells or CNR, for example) had neither been specifically foreseen by Parliament nor expressly provided for in the legislation. And, provided that the particular basic research activity was sufficiently closely connected to recognised therapeutic objectives, it would be covered by the Regulations.[62]

8.15 It is not for us to express an authoritative view on the interpretation of the Regulations. However, it is in the nature of the science that, before research into ES as well as adult stem cells can lead to therapeutic applications, there must be basic research; and, given that the Regulations explicitly recognise the development of treatments for serious diseases as one of the new purposes, it would be perverse if basic research were not implicitly incorporated. The Committee confidently believes that Parliament cannot have intended to will the therapeutic end without also willing the necessary means to that end and has no doubt that the HFEA should consider applications made under the Regulations in accordance with the legal advice it has received. Nevertheless, to put the matter beyond any possible doubt, **when the Government bring forward legislation they should consider making express provision for such basic research as is necessary as a precursor for the development of cell-based therapies.**

Future legislation

8.16 Under the Human Reproductive Cloning Act 2001 placing a CNR embryo in a woman is a criminal offence. Following the Court of Appeal judgment of 18 January 2001, research on CNR embryos is subject to direct regulation by the HFEA. There is an argument that, irrespective of the final outcome of the case, the HFEA retains an indirect form of control over CNR. This is because CNR requires a supply of eggs, and because the storage of eggs is regulated by the HFEA, then to the extent that it involves the storage of eggs CNR falls within the regulatory ambit of the HFEA.

8.17 If the case were to go to the House of Lords and the Government lost the final appeal, there would be a need, as Ministers have acknowledged, for urgent legislation. Even if the Court of Appeal's judgment stands, it is likely that there will be a need for further legislation at a fairly early date to take account of developments that have taken place since 1990.

8.18 The Donaldson report identified a gap in the 1990 Act in that it did not control the mixing of animal eggs with other human cells. It recommended that the mixing of adult

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[60] Ibid.

[61] More recently, Lord Wilberforce's guidance was approved by three of the Law Lords (including Lord Slynn of Hadley giving the leading majority speech) in *Fitzpatrick v Sterling Housing Association Ltd.* [2001] I AC 27. The point at issue in this case was whether the word "family" in the Rent Act 1977 should be extended to cover a same sex partner with regard to enjoying succession rights in relation to statutory tenancies.

[62] In our analysis of this issue we have given "understanding how human stem cells behave and differentiate" as an example of basic research. However, there are other aspects of basic research (for instance, the development and improvement of techniques for extracting ES cells) which can be presented as an essential part of a programme with therapeutic objectives but which are at some (arguably greater) distance from the achievement of these objectives.

(somatic) cells with the live eggs of any animal species should not be permitted, although it did not discuss the thinking behind this recommendation.[63] We are aware of reports of experiments in other countries involving the replacement of a nucleus of an animal egg with the nucleus of an adult human cell. These developments raise important issues. It would clearly be totally unacceptable to implant such an entity in a woman with a view to bringing it to term—and that would be prohibited by the Human Reproductive Cloning Act 2001. For any possible therapeutic applications there would also be significant concerns relating to safety, on which reassurance would be needed. However, if placing a human nucleus in an animal egg provided a way of creating human ES cells for research, some might argue that it was more acceptable to use such an entity for research, the creation of which involves no human gametes, than an embryo created by CNR.

8.19 More generally, the Committee is aware of the very rapid pace at which scientific advances are being made in this field. Only a few years ago the procedure of cell nuclear replacement would hardly have been given credence. It is likely that in the not very distant future there will be further new developments. Some of these possibilities have already been brought to our attention, although publication in reputable journals has not yet occurred in all cases.[64] For example, with greater scientific understanding it may prove possible to:

(a) dedifferentiate an adult stem cell to generate the equivalent of a zygote by growing it in the right conditions, circumventing the need for cell nuclear replacement;

(b) generate an embryo from an oocyte without the need for fertilisation by sperm;

(c) induce the processes of differentiation and redifferentiation more easily using animal rather than human material, for example materials from an animal egg rather than a human egg. Doctors frequently use animal materials in human therapies, but using materials from animal gametes raises separate questions;

(d) induce ES cells to develop into an early embryo (blastocyst) in the laboratory.

8.20 These possible developments raise issues that are beyond our remit. But they clearly need to be kept under review and a separate study of the scientific and ethical implications of using such methods for research in preference to early human embryos may be called for.

Informed consent

8.21 Informed consent is especially important in all research on tissues of human origin. From the evidence we have received, and the people we have talked to informally on our visits, we are satisfied that it is, quite properly, taken very seriously indeed by researchers and by the HFEA. For example, every effort is made to ensure that people undergoing IVF treatment who are invited to donate surplus eggs or embryos for research understand fully what is involved, and that they are given relevant information and the time to consider it. Wherever possible, steps are taken to ensure that the person providing the IVF treatment is not the same as the prospective researcher, to avoid the risk—real or perceived—of moral pressure being brought to bear on potential donors. In the United States people may be paid large amounts of money for gametes, particularly eggs, which makes it much more difficult to ensure that consent is genuinely freely given. **We recommend that the separation of clinical and research roles be standard practice for donation of eggs or embryos. The prohibition in the United Kingdom of payment to donors for gametes has been an important element in preventing undesirable commercialisation of this aspect of assisted reproduction and should be strictly maintained.**

Custody and regulation of stem cell lines

8.22 As explained in Chapter 2, ES cell lines can be grown in culture in principle indefinitely. Three applications have been approved under the 1990 Act which could lead to

[63] Recommendation 6, page 47.

[64] They are discussed in detail by Dr Elizabeth Allan in her written evidence (pp 342-350).

the development of human ES cell lines in the United Kingdom. Applications under the Regulations will almost certainly lead to more ES cell lines being developed in the United Kingdom and lines developed overseas have already been imported. At present responsibility for research using human embryos rests with the HFEA. However, ES cells are not embryos and the HFEA is not responsible under the 1990 Act for ES cell lines. There is consequently considerable urgency in deciding how these lines should be maintained and what degree of regulation, if any, they require.

8.23 We distinguish here between ES cell lines to be used for research and ES cell lines which, may, ultimately, be used for therapeutic purposes. Therapeutic application of ES cells or cells/tissues derived from them is still some way off. If and when it does happen, existing controls will come into operation, including those operated by the Medicines Control Agency.[65] When the prospect of clinical studies involving gene therapy emerged, the Gene Therapy Advisory Committee (GTAC), was established by the Department of Health to provide further oversight of such studies from scientific, medical, safety and ethical standpoints. **The Committee invites the Department of Health to consider either establishing a similar body with oversight of clinical studies involving stem cells, or extending the membership and remit of GTAC to achieve the same ends. The Committee sees no other special need at present for additional regulation of the use of stem cells in the treatment of patients.**

8.24 A more pressing question is what, if any, arrangements are necessary for the oversight of ES cell lines used for research purposes once they have been derived from the embryo. In considering this issue we have been especially concerned to minimise the need to generate new ES cell lines (and consequently minimise the use of embryos for research) while not impeding scientific and medical progress. The Department of Health submitted a supplementary memorandum on the regulation of the use of ES cells.[66]

8.25 The starting point of the Committee's analysis is (as with human embryos themselves) the status of the ES cell lines. They are a human tissue and need to be treated on a similar basis to other human tissues used for research. The sensitivity of using different human tissues varies according to their nature and source. Particular sensitivities attach to certain types of tissue, for example human foetal and embryonic material. However, ES cells once established as a line, are not embryos, and the Committee does not see a need for special arrangements to be made beyond those, such as informed consent (see below), applying to the use of other human material. The logic of this analysis is that the use of established ES cell lines does not require the sort of regulation to which human embryo research is currently subject by the HFEA.

8.26 The Department of Health has asked the Medical Research Council (MRC) to take the lead in considering the establishment of an ES cell bank. Following discussions between the MRC, the Department of Health, the HFEA and other agencies, there is a measure of agreement on the need for such a bank and that the MRC should be responsible for it. The bank would provide scientists with ready access to ES cell lines of guaranteed purity and provenance, and from sources which operate ethically-approved standards. The Department of Health proposes that rules governing what can be deposited in and withdrawn from the bank should be established by a steering committee. Among the matters the rules would cover would be knowledge of the source of the stem cells, obtaining the consent of the donor, and establishing a full history of their storage and handling under good laboratory conditions.

8.27 The Committee believes that the steering committee should also take responsibility for establishing codes of conduct for the use of ES cells, whether obtained from the bank or imported from elsewhere. The bank, should use its best endeavours to ensure that, in addition to ES cells generated in the United Kingdom, it includes ES cell lines of appropriate provenance that have been generated overseas, although we acknowledge that it will not be

[65] Described in the Agency's evidence, pp 256-257.

[66] pp 469-471.

possible (or even appropriate) to obtain all such ES cell lines. Moreover, it would not be practicable, even if it were desirable, to regulate the import by individual scientists of ES cell lines generated overseas, some of which are already in laboratories in the United Kingdom. Such a bank would undoubtedly become the preferred source of ES cells for British scientists. It could also facilitate the distribution of ES cell lines to overseas scientists operating under approved ethical guidelines. It should have the effect of facilitating research and minimising the need both to import ES cells from overseas and to derive new ES cell lines. Above and beyond the proposed steering committee for the stem cell bank, the Committee sees no need for additional levels of regulation.

8.28 If in the future it becomes possible to develop adult stem cell lines, it would be desirable for those lines to be placed in such a bank. In that way stem cell lines could be made available to the widest possible range of reputable researchers and an overview maintained of their use. However, no special consideration needs to be given to regulations for adult stem cells above and beyond those of informed consent (see below).

8.29 **The Committee endorses the Department of Health's proposals to establish a stem cell bank overseen by a steering committee, responsible for the custody of stem cell lines, ensuring their purity and provenance and monitoring their use. As a condition of granting a research licence, the HFEA should require that any ES cell line generated in the United Kingdom in the course of that research is deposited in the bank. Before granting any new licence to establish human ES cell lines, the HFEA should satisfy itself that there are no existing ES cell lines in the bank suitable for the proposed research.**

Informed consent

8.30 Since ES cell lines are potentially "immortal", obtaining informed consent, from those who donate the embryos from which they are derived raises distinctive problems.

8.31 In English law there is no property in live or dead human bodies, with the exception of long dead remains in museums. English law has also hesitated to recognise property in removed body parts: recent case-law does allow for the possibility of B having property rights in A's removed body parts, but it does not directly challenge the orthodox view that A can have no property rights in A's own body parts.[67] Despite this, the principle of respect for persons clearly requires that no human tissue should be taken or used without the informed consent of the donor, or where the tissue is obtained *post mortem,* of the next of kin.

8.32 The culturing of cells and stem cell lines means that a person's genetic identity may be reproduced indefinitely. It has been suggested that those who donate an embryo for stem cell research might subsequently expect a share in any benefits accruing from commercial exploitation of research on stem cell lines derived from it. In our view it would be undesirable for legislation to permit such claims: any commercial benefits will have come about as a result of the research and subsequent development rather than any intrinsic quality of a particular embryo donated. However, it makes it even more important that potential donors should fully understand the implications if embryos they are donating may be used for the production of stem cell lines, and in particular that the material donated may be used for a purpose other than the immediate one.[68]

8.33 **The Committee recommends that the HFEA ensures that the implications arising from the "immortality" of stem cell lines are fully covered in obtaining informed consent from donors giving embryos for the potential establishment of ES cell lines for research. To prevent future restrictions in using ES cell lines (and therefore minimise**

[67] Notably *R v Kelly* [1998] 3 All ER 741.

[68] Three licences have been granted under the Act which could, potentially result in the generation of ES cells. In these cases informed consent would not have been given for purposes other than research into reproduction as this was all that was permitted at the time. The HFEA may wish to work with the scientists involved, and the original embryo donors, to establish whether the donors would give informed consent for use of any ES cells in research permitted under the new purposes.

the need to generate new ES cell lines) the HFEA should not permit ES cell lines to be generated from donated embryos unless informed consent places no specific constraint on their future use. Where parents wish to restrict the type of research which can be undertaken, for example specifically for reproductive purposes, the embryos donated should be used for purposes other than the generation of ES cell lines.

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

Background

1. The Select Committee was appointed in March 2001 to review issues arising out of the Human Fertilisation (Research Purposes) Regulations 2001. The Regulations extended the purposes for which research on human embryos could be undertaken under licence from the Human Fertilisation and Embryology Authority (HFEA) from purposes concerned with reproduction in the Human Fertilisation and Embryology Act 1990 to three additional purposes:

(a) increasing knowledge about the development of embryos,

(b) increasing knowledge about serious disease, or

(c) enabling any such knowledge to be applied in developing treatments for serious disease.

It is important to keep in mind that the Regulations are concerned only with research, not with treatment.

2. The Committee considered a considerable body of oral and written evidence and examined both the scientific and ethical aspects of its terms of reference in depth.

3. Concerns had been expressed about the Regulations on three main grounds:

(a) that they were unnecessary, because developments in adult stem cell research made research on early human embryos unnecessary;

(b) that they were unethical as they permitted the use of early human embryos for wide-ranging research purposes; and

(c) that they represented a significant step on the path to human reproductive cloning.

We examined each of these issues.

Possible alternatives to research on early human embryos

4. Stem cells are cells found in the embryo (ES cells), but also in many parts of the human body, which have the capacity to develop ("differentiate") into different cell types. As such, they have great potential for use in therapies to regenerate tissues in a wide range of serious, but common, diseases. Recent developments in research on adult stem cells have led some to claim that work on ES cells is no longer necessary. We examined in detail the potential of stem cells for developing new therapies and the relative advantages and disadvantages of adult stem cells and ES cells. Adult stem cells have great therapeutic potential and research on them should be strongly encouraged. Nevertheless there is a clear scientific case for continued research on ES cells, in order that the full potential of adult stem cells for therapy can be realised and because it is likely that some therapies will need to use ES cells.

The status of the early embryo

5. The public debate reflects strongly differing views on whether or not the early embryo should be given the full protection due to a person. We set out the arguments in the body of the report. The Committee believes that the issue cannot be looked at in isolation but must take account of the law as it has developed over the last 30 years. That is the background to the Committee's conclusion that whilst respecting the deeply held views of those who regard any research involving the destruction of the early embryo as wrong, and having weighed the ethical arguments carefully, it is not persuaded, especially in the context of the current law and social attitudes, that all research on human embryos should be prohibited.

6. Most research on early embryos uses "surplus" embryos left over from IVF treatment. But the 1990 Act allows embryos to be created for research. The number created has been

much smaller than the number of surplus embryos donated for research. In the Committee's view embryos should not be created specifically for research purposes unless there is a demonstrable and exceptional need that cannot be met by the use of surplus embryos.

7. The 14 days limit on research on early human embryos should remain.

Cell nuclear replacement and cloning

8. Cell nuclear replacement (CNR) involves the replacement of the nucleus of an egg with the nucleus of a cell from another individual (to produce an embryo that is the "clone" of the donor). The implantation of such an embryo in a woman (commonly called "reproductive cloning") was made a specific criminal offence by the Human Reproductive Cloning Act 2001. There have been calls to prohibit the use of CNR for research purposes as well. The majority scientific view seems to be that CNR is more likely to be used as a research tool, which would assist the understanding of the behaviour of adult stem cells and how they might be manipulated, than as the basis for general therapies in its own right. In the Committee's view that is a sufficiently serious and important objective, particularly if the potential of adult stem cells is to be realised, to justify the use of CNR, if licensed by the HFEA, provided that (as with embryos created by IVF for research) embryos are not created by CNR unless there is a demonstrable and exceptional need that cannot be met by the use of surplus embryos.

9. We have examined the issues surrounding reproductive cloning, mainly because of the fear that allowing CNR for research purposes would increase the likelihood of its being used to try to produce a cloned baby. There are very strong scientific and ethical objections to reproductive cloning. The Committee unreservedly endorses the legislative prohibition on it and calls on the Government to support any moves to negotiate an international ban. However, we do not believe that the risk of reproductive cloning is such as to justify prohibiting the use of CNR for research. The HFEA has an excellent record in ensuring that IVF clinics comply with the law, and the Committee is satisfied that its regulatory powers, now reinforced by a specific statutory prohibition, provide sufficient protection against the development of CNR leading to reproductive cloning in the United Kingdom.

Future legislation and regulation

10. The Committee also considered a number of other issues arising out of the Regulations.

Regulation

11. The HFEA's role is crucial to the effective regulation of research on human embryos and the maintenance of public confidence in the regulatory regime. The Government should keep the funding of the HFEA under review and ensure that it is commensurate with its increased responsibilities. It is also important that there should be closer monitoring of the outcomes of research licensed by the HFEA, and the Committee invites the HFEA and the Department of Health to consider how such a review might be undertaken and updated on a regular basis.

The wording of the Regulations

12. There is no definition of "serious disease" in the Regulations, which could cause uncertainty. We invite the Department of Health to draw up guidance on the matter.

13. There is not a perfect match between the basic research on stem cells that currently needs to be undertaken and the wording of the purposes in the Regulations. While the Regulations can be construed without strain so as to encompass basic research, the Government should consider putting the matter beyond doubt when a legislative opportunity arises.

A stem cell bank

14. Stem cell "lines" derived from a single early human embryo can be maintained in culture, in principle indefinitely. As more of these lines are developed it is important that a stem cell bank should be set up for research purposes as a matter of urgency to ensure that there is a single body responsible for the custody of stem cell lines, ensuring their provenance and purity and monitoring their use. In that way stem cell lines can be made widely available to reputable researchers and an overview maintained of their use. Over time this will reduce the need for research on early human embryos.

Informed consent

15. To ensure that informed consent to the donation of embryos for research is freely given—and seen to be freely given—it should be standard practice that the prospective researcher is not the same as the person giving the IVF treatment. The "immortality" of stem cell lines makes the operation of procedures for giving informed consent particularly important where the research is intended to lead to their generation. The Committee recommends that the authorities concerned ensure that the implications arising from the "immortality" of stem cell lines are fully covered in obtaining informed consent from donors.

Conclusions and recommendations

The Committee's detailed conclusions and recommendations are as follows:

STEM CELL RESEARCH

(i) Stem cells appear to have great therapeutic potential for the treatment of many disorders that are both common and serious and for the repair of damaged tissue.

(ii) Until recently most research on stem cells has focussed on ES cells from animals and the derivation of ES cell lines from them; cell lines from human ES cells have the potential to provide a basis for a wide range of therapies.

(iii) Recent research on adult stem cells, including stem cells from the placenta and umbilical cord, also holds promise of therapies; and research on them should be strongly encouraged by funding bodies and the Government.

(iv) To ensure maximum medical benefit it is necessary to keep both routes to therapy open at present since neither alone is likely to meet all therapeutic needs.

(v) For the full therapeutic potential of stem cells, both adult and ES, to be realised, fundamental research on ES cells is necessary, particularly to understand the processes of cell differentiation and dedifferentiation.

(vi) Future developments might eventually make further research on ES cells unnecessary. This is unlikely in the foreseeable future; in the meantime there is a strong scientific and medical case for continued research on human ES cells. *(i-vi paragraph 3.22)*

STATUS OF THE EARLY EMBRYO

(vii) Whilst respecting the deeply held views of those who regard any research involving the destruction of a human embryo as wrong and having weighed the ethical arguments carefully, the Committee is not persuaded, especially in the context of the current law and social attitudes, that all research on early human embryos should be prohibited *(paragraph 4.21)*.

(viii) Fourteen days should remain the limit for research on early embryos. *(paragraph 4.22)*

(ix) Embryos should not be created specifically for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos. *(paragraph 4.28)*

CELL NUCLEAR REPLACEMENT AND CLONING

(x) Basic research is a necessary step to developing treatments and facilitating the potential use of adult stem cells and should be permitted under the Regulations in the same way as more directly applied research to which it is designed to lead, provided that it is subject to strict regulation. *(paragraph 5.4)*

(xi) Although there is a clear distinction between an IVF embryo and an embryo produced by CNR (or other methods) in their method of production, the Committee does not see any ethical difference in their use for research purposes up to the 14 days limit. *(paragraph 5.13)*

(xii) Even if CNR is not itself used directly for many stem cell-based therapies, there is still a powerful case for its use, subject to strict regulation by the HFEA, as a research tool to enable other cell-based therapies to be developed. However, as with embryos created by IVF for research, CNR embryos should not be created for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos. *(paragraph 5.14)*

(xiii) If CNR is permitted in certain limited circumstances, oocyte nucleus transfer should also be allowed for research purposes. *(paragraph 5.20)*

(xiv) Given the high risk of abnormalities the scientific objections to human reproductive cloning are currently overwhelming. *(paragraph 5.21)*

(xv) There are further strong ethical objections in addition to those based on the risk of abnormalities, although not all the arguments deployed against reproductive cloning are equally valid. The most powerful are the unacceptability of experimenting on a human being and the familial and child welfare considerations arising from the ambiguity of the cloned child's relationships. *(paragraph 5.21)*

(xvi) The Committee unreservedly endorses the legislative prohibition on reproductive cloning now contained in the Human Reproductive Cloning Act 2001. *(paragraph 5.21)*

(xvii) The HFEA has an excellent record in ensuring that IVF clinics comply with the law, and we are satisfied that its regulatory powers, now reinforced by a specific statutory prohibition, provide sufficient protection against the development of CNR leading to reproductive cloning in the United Kingdom. *(paragraph 5.24)*

(xviii) The Government should take an active part in any move to negotiate an international ban on human reproductive cloning. *(paragraph 7.22)*

LEGISLATION AND REGULATION

(xix) At an appropriate time, perhaps towards the end of the decade, the Government should undertake a further review of scientific developments, particularly of the

progress of adult stem cell research and therapies, and of the development of stem cell banks, with a view to determining whether research on human embryos is still necessary. *(paragraph 8.4)*

(xx) The Government should keep the funding of the HFEA under review and ensure that its resources are commensurate with its increased responsibilities. *(paragraph 8.5)*

(xxi) The HFEA and the Department of Health should consider how a review of the outcomes of research licensed under the Act might be undertaken and updated on a regular basis *(paragraph 8.6)*

(xxii) The Department of Health should examine with the HFEA the possibility of drawing up indicative guidance as to what constitutes serious disease *(paragraph 8.9)*

(xxiii) When the Government bring forward legislation they should consider making express provision for such basic research as is necessary as a precursor for the development of cell-based therapies *(paragraph 8.15)*

(xxiv) The separation of clinical and research roles should be standard practice for donation of eggs or embryos. The prohibition in the United Kingdom of payment to donors for gametes has been an important element in preventing undesirable commercialisation of this aspect of assisted reproduction and should be strictly maintained *(paragraph 8.21)*

(xxv) The Department of Health should consider either establishing a body similar to the Gene Therapy Advisory Committee with oversight of clinical studies involving stem cells, or extending the membership and remit of GTAC to achieve the same ends. The Committee sees no other special need at present for additional regulation of the use of stem cells in the treatment of patients *(paragraph 8.23)*

(xxvi) The Department of Health's proposals to establish a stem cell bank overseen by a steering committee, responsible for the custody of stem cell lines, ensuring their purity and provenance and monitoring their use, are endorsed. As a condition of granting a research licence, the HFEA should require that any ES cell line generated in the United Kingdom in the course of that research is deposited in the bank. Before granting any new licence to establish human ES cell lines, the HFEA should satisfy itself that there are no existing ES cell lines in the bank suitable for the proposed research. *(paragraph 8.29)*

(xxvii) The HFEA should ensure that the implications arising from the "immortality" of stem cell lines are fully covered in obtaining informed consent from donors giving embryos for the potential establishment of ES cell lines for research. To prevent future restrictions in using ES cell lines (and therefore minimise the need to generate new ES cell lines) the HFEA should not permit ES cell lines be generated from donated embryos unless informed consent places no specific constraint on their future use. Where parents wish to restrict the type of research which can be undertaken, for example specifically for reproductive purposes, the embryos donated should be used for purposes other than the generation of ES cell lines. *(paragraph 8.33)*

APPENDIX 1

Membership

The members of the Committee who conducted this inquiry were:

The Earl of Carnarvon †
Baroness Cumberlege
Lord Dahrendorf
Lord Donoughue
Baroness McIntosh of Hudnall
Baroness Northover
Baroness O'Neill of Bengarve
The Lord Bishop of Oxford (Chairman)
Baroness Perry of Southwark
Baroness Platt of Writtle
Baroness Warwick of Undercliffe

†Deceased. Member of the Committee until 11 September 2001

The Committee appointed as its Specialist Advisers:

Professor Roger Brownsword[69]
Professor Christopher Higgins[70]

Members declared the following interests:

The Earl of Carnarvon—Former Chairman, Agricultural Research Council; Former Chairman, Equine Virology Foundation; Chairman, North Hampshire Medical Fund

Baroness Cumberlege—Member, Council of the Imperial Cancer Research Fund; Chairman, St George's Medical School Council; Member, Council of the University of Sussex; Vice-President, Royal College of Nursing; Vice-President, Royal College of Midwives; Senior Associate, King's Fund; Patron, National Kidney Association; Adviser to National Osteoporosis Society

Lord Dahrendorf—Non-executive director, Glaxo Holdings plc 1984–92

Lord Donoughue—Former Parliamentary Secretary, Ministry of Agriculture, Fisheries and Food

Baroness McIntosh of Hudnall—Trustee, National Endowment for Science, Technology and the Arts (NESTA)

Baroness Northover—Former lecturer in medical history, Wellcome Institute and University College, London; wife of Clinical Director of the ICRF's Bowel Cancer Unit, St Mark's Hospital

Baroness O'Neill of Bengarve—Former member and Chairman of the Human Genetics Advisory Commission; Chairman, Nuffield Foundation; former Chairman, Nuffield Council on Bioethics; Chair, Addenbrooke's Tissue Bank

[69] Professor of Law at the University of Sheffield. He is particularly interested in the regulation and ethical application of new technologies: was co-editor of *Law and Human Genetics: Regulating a Revolution* (Oxford: Hart, 1998); he has written extensively about the morality exclusions in European patent instruments; and, most recently, he has co-authored *Human Dignity in Bioethics and Biolaw* (Oxford: OUP, 2001). Professor Brownsword has also participated in a number of European bioethical projects, including that which led to the so-called Barcelona Declaration, which sets out a scheme of basic principles for ethical science and medicine.

[70] Director of the MRC Clinical Sciences Centre and Head of the Division of Clinical Sciences at Imperial College Faculty of Medicine. Previously he worked for the Imperial Cancer Research Fund and the University of Oxford. His personal research is in cell and molecular biology, particularly the molecular basis of the resistance of cancers to chemotherapy. Although he has not personally worked with stem cells, research on stem cells in animals and on human adult stem cells is undertaken in the Clinical Sciences Centre.

The Lord Bishop of Oxford (Chairman)—Patron, Down's Syndrome Society; Patron, Dyslexia Research Society; Patron, British Epilepsy Association

Baroness Perry of Southwark—Board Member, Addenbrooke's NHS Trust; Chair, Mental Health Committee, Addenbrooke's NHS Trust; Chair, Cambridge Research Governance Committee; Patron, Alzheimer's Research Trust

Baroness Platt of Writtle—Patron, local hospice

Baroness Warwick of Undercliffe—Chief Executive, Universities UK; Member of the Technology Foresight Steering Group

APPENDIX 2

Call for Evidence

On 7 March the House of Lords appointed a Select Committee under the chairmanship of the Bishop of Oxford:

to consider and report on the issues connected with human cloning and stem cell research arising from the Human Fertilisation and Embryology (Research Purposes) Regulations 2001.

The Committee has been asked to report by the end of the year.

The Regulations extend the purposes for which research on early embryos may be carried out from the purposes originally specified in the Human Fertilisation and Embryology Act 1990, such as the treatment of infertility and the development of more effective contraceptive techniques, to the following additional purposes:

- increasing knowledge about the development of embryos
- increasing knowledge about serious disease
- enabling any such knowledge to be applied in developing treatments for serious disease.

The Committee does not propose to review the underlying basis of the 1990 Act, but will examine the ethical, legal, scientific, medical and commercial issues surrounding the Regulations as they now stand. It invites written submissions on all matters relevant to them, but in particular on the following questions :

1. Do the additional purposes in the 2001 Regulations raise issues of principle different from the purposes specified in the 1990 Act?
2. There is a range of different views world-wide on the acceptability of research on embryonic stem cells. What considerations underlie these differences? Do changes in the law here have implications for practice overseas and vice versa?
3. Have increased globalisation and other international commercial developments, in relation, for example, to e-commerce and patenting, changed the context of the debate in the UK? Would issues relating to research on embryos benefit from more attention at international level?
4. What are the potential medical benefits of stem cell research? What is the most likely time-scale for realising them? What are the potential risks?
5. There are differing views on the extent to which potential treatments could be developed from non-embryonic stem cells, such as adult and umbilical cord stem cells. What are the advantages and disadvantages of working with these alternative sources of stem cells?
6. What are the commercial interests involved in research in this area? Does increased commercial involvement create additional ethical difficulties?
7. Human reproductive cloning (the transfer of an embryo created by cell nuclear replacement into a woman's uterus) is unlawful in the UK, and the Government has announced its intention of reinforcing this ban by specific primary legislation. Is there likely to be any pressure to resist such a ban? What are the principal ethical (and scientific) arguments against human reproductive cloning?
8. Does the extension of embryonic stem cell research, and, in particular, the technique of cell nuclear replacement therapy (therapeutic cloning) - designed to grow tissue for therapeutic purposes - increase the likelihood of human reproductive cloning in the future?
9. Has the regulatory framework established by the 1990 Act operated effectively? Is it likely to remain adequate for the foreseeable future? Have any gaps appeared in the regime as a result of developments since 1990?
10. Do additional guidelines need to be developed to assist the Human Fertilisation and Embryology Authority in issuing licences in accordance with the new Regulations? If so, what should the guidelines contain?

5 April 2001

APPENDIX 3

Organisations and individuals who gave evidence

The following witnesses submitted written evidence. Those marked * also gave oral evidence.

Organisations

Academy of Medical Sciences*

All-Party Parliamentary Pro-life Group

Assisted Conception Unit, Birmingham Women's Health Care

Association of Lawyers for the Defence of the Unborn

Association of Medical Research Charities*

Bahá'í Community of the United Kingdom

Baptists for Life Inc

BioIndustry Association*

Biotechnology and Biological Sciences Research Council (BBSRC)

Board for Social Responsibility of the Church of England*

British Heart Foundation

British Medical Association (BMA)

Cambridge University Orthodox Society

Christian Action Research and Education (CARE)*

Catholic Union of Great Britain and Guild of Catholic Doctors

Centre for Bioethics and Public Policy

Comment on Reproductive Ethics (CORE)

Corner House

Council of Heads of Medical Schools & Deans of UK Faculties of Medicine

Court of the Chief Rabbi*

Diabetes UK

Fisher Society

Genetic Interest Group*

(Members of the) German Parliament's Committee of Inquiry on Law and Ethics of Modern Medicine

Department of Health*

Human Fertilisation and Embryology Authority*

Human Genetics Alert

IMAGE

Institute of Science in Society

Islamic Medical Association*

King's College London

LIFE

Linacre Centre for Healthcare Ethics*

Medical Ethics Alliance

Medicines Control Agency

Medical Research Council*

Movement against the Cloning of Humans (MATCH)

Nuffield Council on Bioethics*

Parkinson's Disease Society*

Policy, Ethics and Life Sciences Research Institute (PEALS), Universities of Durham and Newcastle

Primary Immunodeficiency Association (PiA)

ProLife Alliance

Roslin Institute*

Royal Society*

Royal Society of Edinburgh

Scientists for Labour

Society for the Protection of Unborn Children (SPUC)*

Special Parkinson's Research Interest Group (SPRING)

StudentLifeNet

United Free Church of Scotland

University Faculty for Life (UFL)

Wellcome Trust*

Individuals

Dr Ilham Saleh Abuljadayel

Dr Elizabeth Allan

Lord Alton of Liverpool*

Dr Michael Antoniou*

Rupert Beale and Michael Pacold

The Rev Ian Benson

Dr Caroline Berry

Professor Helen M Blau

The Rt Rev Christopher Budd

Mrs Elizabeth A Burbage

Professor Derek Burke

Eileen Cole

Mrs J E Coverdale

Norman Dallen

Alison Davis*

Ian Duncan

Francis Etheredge

Dr Jonas Frisen

Lord Habgood

Professor John Harris

Colin Harte

David Heale

The Rt Rev Christopher Herbert

Christopher W J Hill

A D Hunter

Dr Gavin E Jarvis

Professor Peter Jeffery

Kathleen Liddell

Dr Faith Lockwood

Dr Kirsten McCoull and 17 others

The Rev J MacDonald Smith

Dr Maureen McHugh

Professor Sheila A M McLean

Professor Peter H Millard

Sue Moore

G E New

Mrs M E Newman and D Hoggart

Richard Ora

John Perkins

Jean Plant

Professor David A Prentice*

Professor Hilary Rose

Professor Nadia Rosenthal

Peter Saunders

Professor Neil Scolding*

Dr Austin Smith

Sir Richard Sykes*

Lord Tombs

Professor Angelo Vescovi

Lord Walton of Detchant*

Dr Paul Watt

Gareth Williams*

His Eminence Cardinal Thomas Winning and His Eminence Cardinal Cormac Murphy-O'Connor

Professor John Wyatt

Mr A L & Mrs D E Young

Miss Naomi Young

Philip Young

APPENDIX 4

The moral status of the early embryo: reading the Christian tradition

The question of research on embryos did not arise before the late 20th century. The moral status of the early embryo in the Christian tradition has therefore to be deduced from attitudes to abortion.

In the Christian tradition abortion at any stage has always been regarded as gravely sinful. However, for many centuries the termination of a pregnancy at an early stage carried lesser penalties than one later. This was related to the view that the human soul did not enter the embryo ("ensoulment") until 40 days after conception in the case of a man, and 90 days after conception in the case of a woman, an understanding that was taken over from Aristotle. This distinction in the seriousness of early and late abortion was grounded in the Greek and early Latin translations of Exodus 21, 22 which drew a distinction between the formed and unformed foetus.

These distinctions became the established position from at least the 12th to the 17th centuries and are present in significant Western writings of earlier periods. The evidence of the earliest Christian centuries is open to different interpretations on this issue. The Eastern Church, however, does not acknowledge such gradations in the seriousness of abortion.

In 1869 Pope Pius IX declared that all mothers who had survived an abortion were to be excommunicated making no reference to the earlier distinction between animate and un-animate foetuses and implying that a person was ensouled from conception onwards. For many Christians today, not just Roman Catholics, this position is definitive because, with the outmoding of the Aristotelian concept of delayed ensoulment, fertilisation is the point at which human life emerges and, as vulnerable human life, it is particularly worthy of protection. Many theologians take the view that, because the early embryo may be a person and because this is such a crucial matter, the embryo must be given the benefit of any doubt and there is therefore a moral obligation to offer all the protection that would be accorded a baby or adult.

For other Christians, however, the fact that the Christian tradition, for so much of its history, made a distinction between the moral status of the unformed and the formed embryo, and thought of the human person in the full sense coming only with a delayed ensoulment, remains significant: it reflects a valid moral distinction which needs to be affirmed even with the outmoding of the Aristotelian philosophy on which it was once based.

APPENDIX 5

Glossary of biological terms used in the Report

blastocyst:	a hollow ball of 50 to 100 cells reached after about five days' embryonic development just before implantation in the uterus.
cell line:	cells of common descent and type cultured in the laboratory.
cell nuclear replacement:	(also called somatic cell nuclear transfer) the procedure of replacing the cell nucleus of an egg with the nucleus from another cell.
cell type:	one of over 200 different types of cells in the body, for example blood cells, liver cells, neural cells. Each of these cell types has a different subset of genes switched on ("expressed") and therefore specific characteristics which allow it to serve a specific function in the body.
clone:	a cell or organism derived from and genetically identical to another cell or organism.
cytoplasm:	a jelly-like substance, which together with the nucleus which it surrounds, forms the cell.
dedifferentiation:	the process of inducing a specialised cell to revert towards pluripotency.
differentiation:	the process by which less specialised cells develop into more specialised cell types—see Box 1 in Chapter 2.
DNA:	deoxyribonucleic acid—the cell's and the body's genetic material.
enrichment:	increasing the proportion of stem cells in a tissue sample by removing some of the non-stem cell material.
enucleated:	from which the nucleus has been removed (usually of an egg).
gamete:	the male sperm or female egg.
genome:	the complete genetic material of an individual.
in vitro *fertilisation:*	the fertilisation of an egg by a sperm outside the body.
mitochondria:	energy-producing structures in the cytoplasm of a cell.
multipotent:	having the capacity to develop into multiple (but not all) cell types.
oocyte:	the female egg.
plasticity:	the capacity of cells to develop into different cell types.
pluripotent:	having the capacity to develop into every cell type in the human body, but not the extra-embryonic tissues such as the placenta and umbilical cord.
primitive streak:	a collection of cells which appears at about 14 days after fertilisation from which the central nervous system eventually develops.
redifferentiation:	the process of inducing a dedifferentiated cell to differentiate into a (different) specialised cell type.
totipotent:	having the capacity to develop into every cell type required for human development, including extra-embryonic tissues.
zygote:	the single cell formed when the male sperm fertilises the female egg.

APPENDIX 6

Reproductive Cloning

1. There is widespread opposition to reproductive cloning. In a report published very soon after the announcement of the birth of Dolly the sheep the House of Commons Select Committee on Science and Technology recommended that "the intention of Parliament to ban human cloning should be reaffirmed. We believe that it would be possible to produce a formula which would effectively ban cloning a human through primary legislation."[71] In its response the Government said that "it would consider carefully in the light of developments, whether the legislation needs to be strengthened in any more specific way".[72] Subsequently the Government announced on several occasions, that they would introduce legislation to prohibit reproductive cloning, and a commitment to that effect was included in the Labour Party's 2001 Election Manifesto. Until the judicial review they thought that the practice was already unlawful on the ground that it would require a licence from the HFEA, which had made it clear that it would not grant one. Cloning a child without a licence would be a criminal offence. In the event, as explained in Chapter 1, the Government's hand was forced by the High Court judgment in the judicial review and they introduced emergency legislation, which became the Human Reproductive Cloning Act 2001.

The scientific and medical considerations

2. The scientific objections to reproductive cloning are currently overwhelming. It required 277 attempts to produce Dolly the sheep, and it might prove even more difficult in humans. It would be unthinkable to allow that degree of experimentation on a human being. Moreover, the consequences of producing cloned animals are still not well understood: in recent studies there has been a high rate of malformations, and premature death. Many clones are also excessively large. This is not just a scientific issue—it would be unethical to attempt to produce a cloned baby, given the high risk of abnormalities.

Ethical considerations

3. It is possible that in time the scientific difficulties could be overcome (as a result of work on animals, although ultimately the procedure would have to be tested on human beings). If so, what then should society's attitude be? It is often claimed that reproductive cloning is contrary to human dignity. For example, article 11 of the UNESCO Universal Declaration on the Human Genome and Human Rights states that "practices that are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted". But the concept of human dignity is ill-defined, and it is desirable to try to identify more precisely the reasons which underlie the deeply held and widespread aversion to the idea.

4. One argument that has been advanced is that it could be used for highly undesirable and immoral purposes. The European Parliament passed a resolution in March 1997, whose preamble states that "the cloning... of human beings cannot under any circumstances be justified or tolerated by any society, because it is a serious violation of fundamental human rights and is contrary to the principle of equality of human beings, as it permits a eugenic and racist selection of the human race, it offends against human dignity and it requires experimentation on humans". It is indisputable that reproductive cloning should not be used for racist or eugenic purposes, but to the Committee's knowledge no one outside the world of science fiction has suggested that it should be. And the fact that a technique could be used for improper purposes is not in itself a sufficient reason for prohibiting it.

5. A more commonly expressed view is that the underlying objection to reproductive cloning is a person's right to a "genetic identity". The European Parliament's 1997 resolution asserted that every individual has the right to his or her own genetic identity. As has often been pointed out, this cannot be an absolute right, since identical twins share a genetic identity and no one suggests that they have less of a personal identity or a lower worth. But there is an obvious distinction between identical twins and a cloned child, in that the twins' genetic identity is given, whereas that of the cloned child would have been chosen for it by the person whose cell had been cloned (or the person who had decided whose cell should be used for the purpose).

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[71] *Fifth Report, Session 1996-97: The Cloning of Animals from Adult Cells*, March 1997, HC 373-E.

[72] Cm 3815.

6. This leads to what we see as the strongest set of arguments against reproductive cloning—the familial and child welfare considerations. Those who advocate reproductive cloning do so on the ground that it would provide an opportunity for a couple who could not have a child normally, by gamete[73] donation or by IVF to have a child with the inherited genes of at least one of them. The expectation therefore would be that a cell nucleus from one of the parents would be used. This would give rise to a whole range of ambiguous relationships to other members of the child's family. If the cell nucleus from the father were used, for example, the child would be the genetic son of its grandparents, the genetic sibling of its uncles and aunts and the genetic uncle of its cousins. The range of ambiguities introduced into family relationships by cloning from a close relative would be large and the possibility for emotional confusion and uncertainty—not only on the part of the cloned child—considerable.

7. Sometimes parents are said to want to clone a child who has died. While this may be an understandable reaction to the devastating loss of a child, it represents a misconception that the cloned child would be the same as the dead child because it was genetically identical to it. It would in fact be likely to be very different as a result of different environmental factors, but would have to live with the unavoidable expectation that it was intended to replace a lost child and was not brought into being for its own sake.

8. It might be argued that these familial objections would be overcome if the child were cloned from a stranger, but it is difficult to see what the object would be in that case, since such pressure as there is for allowing reproductive cloning comes from those who are desperate to have a child with a genetic link to at least one of the parents.

9. Against this it is argued that reproductive cloning is simply another form of infertility treatment and that people have a right to reproduce themselves and by extension to secure this right by whatever means is technically feasible. Such a right has not been established in law and there would be strong objections to it, since it would assert a right on the part of the parents at the expense of consideration of the welfare of the child. There have always been people who, sadly, have had to accept that they cannot have children genetically related to them, and seeking to meet their needs should not take priority over the considerable scientific and ethical risks inherent in permitting reproductive cloning.

[73] Male sperm and female eggs.

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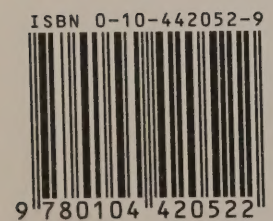

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